Official Title of Study:

A Clinical Study to Evaluate the Steady State Pharmacokinetics of Baraclude in Participants with Hepatitis B Virus Infection

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Clinical Protocol AI463528

A Clinical Study to Evaluate the Steady State Pharmacokinetics of Baraclude in Participants with Hepatitis B Virus Infection

Revised Protocol Number: 01
Incorporates amendment(s) 01

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	27-Mar-2017	Incorporates Amendment 01
Amendment 01	27-Mar-2017	Changes to Protocol include: • According to the regulation for non-registrational study in Japan, changed the word from "GCP" to "Ethical Guidelines for Medical and Health Research Involving Human Subjects". • Added some clarifications.
Original Protocol	22-Feb-2017	Not applicable

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1 SYNOPSIS

Protocol Title: A Clinical Study to Evaluate the Steady State Pharmacokinetics of Baraclude in Participants with Hepatitis B Virus Infection

Study Phase: IV (post-marketing)

Rationale:

While pharmacokinetics of Baraclude® has been investigated in the global HBV clinical trial population, pharmacokinetic (PK) information specifically for Japanese patients diagnosed with HBV infection has not been studied. Such pharmacokinetic information may provide a better understanding of Baraclude in a real-world clinical setting in Japan.

Study Population:

Inclusion Criteria

a) Participants with chronic hepatitis B (CHB) (excluding participants with a superinfection) who have been confirmed to have CHB by one of the following:

   i) Detectable Hepatitis B surface antigen (HBsAg) at screening and for at least 24 weeks prior to screening or detectable HBsAg for < 24 weeks and negative for IgM core antibody and confirmation of chronic hepatitis on liver biopsy

   ii) Documentation of positive Hepatitis e antigen (HBeAg) status at screening and at least once ≥ 4 weeks prior to screening

b) Participants whose condition is stable in the investigator's judgement

c) Participants who are being treated with 0.5 mg daily of Baraclude for a minimum of 10 consecutive days prior to the study enrollment

d) Creatinine clearance is > 50 mL/min

Exclusion Criteria

a) Lamivudine-refractory participants

b) Any significant, acute illness or chronic medical illness that is not stable and/or untreated

c) Current or recent (within 3 months of Baraclude administration) gastrointestinal disease that could impact upon the absorption of study drug

d) Any gastrointestinal surgery that could impact upon the absorption of study drug

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

Objectives and Endpoints:

Objective	Endpoint
Primary	

Objective	Endpoint
• to evaluate the steady state of Baraclude pharmacokinetics in HBV-infected participants	• pharmacokinetic parameter values derived from plasma concentration versus time data using non-compartmental methods
Secondary	
• Not applicable	• Not applicable.

Overall Design:

This is an open label, single-dose, steady state pharmacokinetics (PK) study of Baraclude in Japanese HBV-infected participants. Participants will undergo a screening evaluation to determine eligibility within 21 days prior to administration of study drug. Participants will be admitted into the clinical site prior to study drug administration. On this day (Day 1), Baraclude will be administered, and breakfast will be provided 2 hours after administration.

Participants will remain at the clinical site for approximately 2 days following administration of the single dose of study medication. The initial time of dose administration will be called "0" hour. At the time of dosing, 240 mL of water will be administered to the participants with the dose.

PK samples will be taken as described in the Schedule of Activities.

The study design schematic is presented in Table below.

Study Schematic

Day -21 or Later	Day 1	Day 2
Screening and Enrollment Laboratory assessments	Treatment with Baraclude PK Assessments	PK Assessment Study discharge

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at screening. Blood samples will be collected for up to 24 hours after study drug administration for pharmacokinetic (PK) analysis. Participants will be closely monitored for adverse events throughout the study.

Number of Participants:

Approximately 8 participants will be enrolled.

Treatment Arms and Duration:

Participants will take 1 dose of 0.5 mg Baraclude in the clinic facility on Day 1. The local marketed Baraclude will be used as study treatment in this study. Approximately 2 days after Baraclude administration, participants will leave the clinical site if they have not experienced any adverse events or are in a condition to be released according to the investigator's clinical judgement. The approximate duration of this study is 2 days plus up to 3 weeks for the screening period.

Study treatment:

Study Drug for AI463528		
Medication	**Potency**	**IP/Non-IP**
Baraclude	0.5 mg	IP

2. SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (AI463528)

Procedure	Screening Day -21 Visit	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X	
Medical History	X	Include any toxicities or allergy related to previous treatments.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes body temperature, respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection.
Concomitant Medication Use	X	
Electrocardiogram (ECGs)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests		
Serology	X	Includes hepatitis C antibody, HIV-1 and -2 antibody, and CrCl.
Pregnancy Test	X	For WOCBP only. Urine or serum.
Serum creatinine	X	
Adverse Event Reporting		
Monitor for Serious Adverse Events		All SAEs must be collected from the date of participant's written consent until 30 days after discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time

Table 2-2: On Treatment Procedural Outline(AI463528)

Procedure	Day 1	Study Discharge	Notes
Safety Assessments			
Physical Examination (PE)	X		
Physical Measurements	X		Weight only
Vital Signs	X		Includes body temperature, respiratory rate, and seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection.
Concomitant Medication Use	X		
Adverse Event Reporting			
Monitor for Adverse Events and Serious Adverse Events	X	X	See note in screening procedures.
Pharmacokinetic (PK) Assessments			
Serial Blood PK Sampling	X	X	See Section 9.5.
Clinical Drug Supplies			
Study Drug Administration	X		Supplied by the participant.

Abbreviations: D=Day

3. INTRODUCTION

Chronic infection with Hepatitis B Virus (HBV) is a cause of substantial morbidity and mortality, around the world. Approximately 350 to 400 million people worldwide have chronic hepatitis B (CHB) infection,[1,2] and over 1 million people die each year from complications of cirrhosis and primary hepatocellular carcinoma (HCC).[3]

HBV genomic sequences have been classified into at least eight genotypes (A through H) based on a divergence of 8% or more over the complete nucleotide sequence.[4,5] These genotypes vary worldwide and have distinct geographic distributions.[6,7,8] Japanese patients with chronic HBV infection often have genotypes B and C[9] whereas those with acute infection are more likely to have genotype A.[10,11] In addition, studies suggest that acute infection with HBV genotype A may be associated with an increased risk of progression to persistent infection.[12]

Chronic intrahepatic replication of HBV also appears to be a critical event in the pathogenesis of liver injury, and results in an ongoing cascade of inflammation, injury, and repair. This recurring inflammatory cycle leads to scarring (fibrosis), progression to cirrhosis, and to dysregulation of hepatocyte regeneration with the potential for HCC.

Intrahepatic replication of the virus appears to be a critical factor in HBV disease progression. A meta-analysis of epidemiology studies concluded that the risk for HCC increased 20-fold for individuals who were hepatitis B surface antigen (HBsAg)-positive compared with those who were HBsAg-negative.[13] Another study found that, compared to HBsAg-negative controls, the relative risk for HCC was 9.6 in HBsAg-positive patients and 60.2 in those who were also HBeAg-positive.[14] These data suggest that optimal anti-HBV therapy would provide sustained inhibition of viral replication, leading to improved clinical outcomes. A direct link between antiviral therapy and clinical outcome was established in a 32-month study in which continuous treatment with lamivudine (LVD) approximately halved the rate of hepatic decompensation and reduced the risk of HCC among patients with CHB infection and advanced fibrosis or cirrhosis at baseline.[15]

Approved therapies for CHB infection include interferon alfa, peginterferon alfa-2a,[16] LVD,[17] adefovir dipivoxil (ADV),[18] Baraclude® (entecavir), telbivudine (LdT), and tenofovir disoproxyl fumarate (TDF).[19] The recombinant alfa interferons act primarily as endogenous immunomodulatory agents and also have intrinsic antiviral effects. Interferon is administered by injection and is frequently associated with fever, flu-like symptoms, neutropenia, and depression. Lamivudine, ADV, LdT, TDF, and Baraclude are nucleoside analogs (NAs) that directly inhibit viral replication. Lamivudine is well tolerated, but efficacy is limited by resistance, which develops at a rate of 15% to 25% during the first year of treatment and up to 70% after 4 years of treatment.[20] The emergence of lamivudine-resistant (LVDr) virus is usually associated with renewed HBV replication and a subsequent reduction in clinical efficacy.[21] Among subjects with pre-existing LVDr, rates of ADV resistance (ADVr) are reported to be 18% after 1 year and 25% after 2 years

of therapy.[22,23] Adefovir therapy is associated with a potential risk of nephrotoxicity.[18] The efficacy of LdT was demonstrated in Phase 3 controlled study of nucleoside-naive subjects with HBeAg-positive or HBeAg-negative HBV infection. Genotypic analysis detected amino acid substitutions associated with virologic failure in 49 of 103 HBeAg-positive subjects and 12 of 12 HBeAg-negative subjects after ≥ 16 weeks of treatment.[19] Tenofovir is approved for the treatment of CHB based on the results of 2 Phase 3 controlled studies in HBeAg-positive and HBeAg-negative subjects.[24]

Overall, based on the efficacy and safety results of Phase 2/3 studies of Baraclude vs LVD, a Phase 3b study of Baraclude vs ADV in CHB patients with compensated liver disease, and a Phase 3b study of Baraclude vs ADV in patients with decompensated liver disease, as well as pediatric studies, Baraclude is an important treatment option among available oral HBV therapies

3.1 Study Rationale

While pharmacokinetics of Baraclude has been investigated in the global HBV clinical trial population, pharmacokinetic (PK) information specifically for Japanese patients diagnosed with HBV infection has not been studied. Such pharmacokinetic information may provide a better understanding of Baraclude in a real world clinical setting in Japan.

3.2 Background

3.2.1 Pharmacology

For physical/chemical and pharmaceutical properties and formulation, refer to the Investigator Brochure Section 3.[25]

3.2.2 Toxicity

Dose-related systemic exposures to Baraclude were established after multiple doses in nonclinical toxicology species. Mean steady-state exposures in toxicology studies ≥ 3 months in duration were up to 2,500 times greater than the mean steady-state exposure in humans at 1.0 mg.

3.2.3 Preclinical Metabolism and Pharmacokinetics

Mechanism of Action

Baraclude is efficiently phosphorylated to entecavir (ETV)-TP by cellular nucleoside kinases. By competing directly with the natural substrate, dGTP, ETV-TP functionally inhibits all 3 activities of the viral polymerase: (1) priming of the HBV polymerase; (2) reverse transcription negative strand DNA synthesis; and (3) DNA polymerase activity responsible for positive strand DNA synthesis.

Entecavir-triphosphate has > 15-fold and > 30-fold potency than the active phosphorylated forms of LVD and ADV, respectively, in inhibiting polymerization.[26]

In Vitro Antiviral Activity

Baraclude inhibited HBV DNA synthesis (EC50) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC50 value for Baraclude against LVDr HBV (rtM204V, rtL180M) was 0.026 μM (range 0.010-0.059 μM).[27,28,29,30]

3.2.4 Pharmacokinetics of Baraclude

In healthy subjects, Baraclude was rapidly absorbed, with peak plasma concentrations occurring between 0.5 and 1.5 hours. There was a dose-proportionate increase in peak plasma concentration (Cmax) and area under concentration-time curve (AUC) values following multiple doses ranging from 0.1 to 1 mg. Steady-state was achieved after 6-10 days of once daily (QD) dosing with approximately 2-fold accumulation. Maximum observed concentration and trough plasma concentration at steady state were 4.2 and 0.3 ng/mL, respectively, for a 0.5-mg dose, and 8.2 and 0.5 ng/mL, respectively, for a 1 mg dose. In healthy subjects, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.[31,32,33]

Oral administration of Baraclude 0.5 mg with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a minimal delay in absorption (1-1.5 hour fed vs 0.75 hour fasted), a decrease in Cmax of 44% to 46%, and a decrease in AUC of 18% to 20%.[34,35]

The estimated volume of distribution for Baraclude was in excess of total body water, suggesting that it has good penetration into tissues. Protein binding to human serum protein in vitro was approximately 13%.[31,33,36]

Baraclude is not a substrate, inhibitor, or inducer of the cytochrome P-450 (CYP450) enzyme system. Following administration of 14C-ETV in humans and rats, no oxidative or acetylated metabolites and minor amounts of Phase 2 metabolites (glucuronide and sulfate conjugates) were observed.[33,37,38,39,40] After reaching peak levels, Baraclude plasma concentrations decreased in a bi-exponential manner with a terminal elimination half-life of approximately 128-149 hours. The observed drug accumulation index is approximately 2-fold with daily dosing, suggesting an effective accumulation half-life of about 24 hours.[31,33]

Baraclude is predominantly eliminated by the kidney, with urinary recovery of unchanged drug at steady-state ranging from 62% to 73% of the dose. Renal clearance is independent of dose and ranges between 360 and 471 mL/min suggesting that Baraclude undergoes both glomerular filtration and net tubular secretion.[31,33]

3.3 Benefit/Risk Assessment

Baraclude has been approved for the treatment of HBV in Japan since 2006. Participants in this study routinely take Baraclude as part of their daily medication for the management of HBV; therefore, there is no additional risk. In this study, participants will experience 12 venipunctures for blood draws for screening assessments and PK assessments. There is a small risk of infection with each venipuncture. The data collected from this study will add to the understanding of real-world use of Baraclude in HBV Participants in Japan.

4. OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • to evaluate the steady state of Baraclude pharmacokinetics in HBV-infected participants	• pharmacokinetic parameter values derived from plasma concentration versus time data using non-compartmental methods
Secondary • Not applicable.	• Not applicable
Tertiary/Exploratory • Not applicable	• Not applicable

5. STUDY DESIGN

5.1 Overall Design

This is an open-label, single-dose, steady state pharmacokinetics (PK) study of Baraclude in Japanese HBV participants. Participants will undergo a screening evaluation to determine eligibility within 21 days prior to administration of study drug. Participants will be admitted into the clinical site prior to study drug administration. On this day (Day 1), Baraclude will be administered, and breakfast will be provided 2 hours after administration.

Participants will remain at the clinical site for approximately 2 days following administration of the single dose of study medication. The initial time of dose administration will be called “0” hour. At the time of dosing, 240 mL of water will be administered to the participants with the dose.

Participants will take 1 dose of 0.5 mg Baraclude in the clinic facility on Day 1. The local marketed Baraclude will be used as study treatment in this study. PK samples will be taken as described in Table 9.5-1. Approximately 2 days after Baraclude administration, participants will leave the clinical site if they have not experienced any adverse events or are in a condition to be released according to the investigator’s clinical judgement. The approximate duration of this study is 2 days and up to 3 weeks for the screening period.

Participants are asked to take Baraclude once daily at the same time in the day (eg, 9:00AM) for 10 days before entering the clinical site.

The study design schematic is presented in Table 5.1-1.

Table 5.1-1: Study Schematic

Day -21 or Later	Day 1	Day 2
Screening and Enrollment Laboratory assessments	Treatment with Baraclude PK Assessments	PK Assessment Study discharge

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at screening. Blood samples will be collected for up to 24 hours after study drug administration for pharmacokinetic (PK) analysis. Approximately 30 mL of blood will be drawn from each participant for screening assessments (8 mL) and PK assessments (22 mL) during the study. Participants will be closely monitored for adverse events throughout the study.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

Approximately 8 participants will be enrolled.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last visit. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

The endpoints selected for this study are to determine the steady state pharmacokinetics of Baraclude when Baraclude is administered to real-world HBV-infected participants in Japan. Participants enrolled in this study are expected to achieve steady state prior to the start of the study; therefore, a single dose of Baraclude will provide the necessary information to assess the primary objective.

5.5 Justification for Dose

The dose selected for this study is 0.5 mg of Baraclude, based on current prescribing information in the label.

6. STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Informed consent forms voluntarily signed by participants including consent for screening procedures to confirm eligibility shall be obtained prior to their enrollment in the study

2) Type of Participant and Target Disease Characteristics

a) Participants with chronic hepatitis B (CHB) (excluding participants with a superinfection) who have been confirmed to have CHB by one of the following:

i) Detectable HBsAg at screening and for at least 24 weeks prior to screening or detectable HBsAg for < 24 weeks and negative for IgM core antibody and confirmation of chronic hepatitis on liver biopsy

ii) Documentation of positive Hepatitis e antigen (HBeAg) status at screening and at least once ≥ 4 weeks prior to screening

b) Participants whose condition is stable in the investigator's judgement

c) Participants who are being treated with 0.5 mg daily Baraclude for a minimum of 10 consecutive days prior to the study enrollment

d) Creatinine clearance is > 50 mL/min

e) Body mass index (BMI) of 18.5 to 30 kg/m^2 (BMI = body weight [kg]/height $[m]^2$)

3) Age and Reproductive Status

a) Males and Females, ages 20 or age of majority to 70 years, inclusive

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) during the screening period.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s), Baraclude, plus 5 half-lives of study treatment Baraclude (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days post-treatment completion

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s), Baraclude, plus 5 half-lives of the study treatment (5 days) plus 90 days (duration of sperm turnover) for a total of 95 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4 which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Lamivudine-refractory participants

b) Any significant, acute illness or chronic medical illness that is not stable and/or untreated

c) Current or recent (within 3 months of Baraclude administration) gastrointestinal disease that could impact upon the absorption of study drug

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

e) Any gastrointestinal surgery that could impact upon the absorption of study drug

f) Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study drug administration (within 2 weeks for plasma only)

g) Blood transfusion within 4 weeks of study drug administration

h) Inability to tolerate oral medication

i) Inability to be venipunctured and/or tolerate venous access
j) Smoking more than 10 cigarettes per day
k) Recent (within 6 months of study drug administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 5)
l) Any other sound medical, psychiatric and/or social reason as determined by the investigator

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7, Concomitant Therapy.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population
b) Any of the following on 12-lead electrocardiogram (ECG) prior to study drug administration, confirmed by repeat
   i) PR ≥210 msec
   ii) QRS ≥ 120 msec
   iii) QT ≥ 500 msec
   iv) QTcF ≥ 450 msec
c) Positive blood screen for hepatitis C antibody or HIV-1 and -2 antibody

4) Allergies and Adverse Drug Reaction

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

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
c) Inability to comply with restrictions as listed in Section 6.3, Lifestyle Restrictions
d) Discretion of the investigator

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

1) Participants are to refrain from strenuous exercise, contact sports, and sunbathing from at least 1 day prior to the day of study dosing until study discharge.
2) Participants are not permitted to consume alcohol-containing beverages from 3 days prior to the day of study dosing until study discharge.
3) Participants are not permitted to smoke while residing at the clinical facility.

4) Participants are required to remain in the clinical facility at least 24 hours after dosing during or until furloughed.
5) Participants may not drink water one hour before and after study drug administration except with dosing. Water may be consumed ad libitum at other times.
6) Participants are required to fast (nothing to eat or drink except water) for 10 hours prior until 2 hours after study drug administration.
7) Participants should maintain an upright (seated or standing) position for at least 4 hours post-dose.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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, 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 does not permit the re-enrollment of a participant that has discontinued the study as a pre-treatment failure.

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will not be permitted (this does not include parameters that require a confirmatory result).

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:

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

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.

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
Baraclude	0.5 mg	1 dose at 9:00 am of Day 1 (± 30 minutes)	oral

The local marketed Baraclude will be used as study treatment in this study.

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

7.2 Method of Treatment Assignment

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001 (eg, 00001, 00002, 00003.... 00010). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed and undergo PK sampling.

7.3 Blinding

Not applicable.

7.4 Dosage Modification

Participants will receive a single dose of Baraclude 0.5 mg. No dose modifications are permitted during the conduct of the study or for 10 days prior to Day 1.

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

Not applicable.

7.6 Treatment Compliance

Study drug will be administered in the clinical facility. After administration of Baraclude, a mouth check will be performed to verify that the participant has swallowed the dose.

7.7 Concomitant Therapy

Please follow guidance on concomitant therapy in the Japanese package insert.

7.7.1 Prohibited and/or Restricted Treatments

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

1) Exposure to any investigational drug or placebo within 4 weeks of study drug administration.
2) Use of any prescription drugs or over-the-counter acid controllers within 4 weeks prior to study drug administration except those medications cleared by the BMS medical monitor.
3) Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to study drug administration except those medications cleared by the BMS medical monitor.
4) There should be no changes to the medications and/or dosages of those medications used to manage chronic illnesses for 10 days prior to Day 1 and during Day 1.

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

The investigator should contact and confirm agreement with the BMS medical monitor (and acknowledgement from the contract research organization medical monitor) prior to the administration of any concomitant medications.

7.8 Treatment After the End of the Study

At the end of the study/Period (approximately 2 days), 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.

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 involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

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 notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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 (CRF) page.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

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 CRF 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

Not applicable.

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, surrogate, or the participant's legally authorized representative).

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 30 days after discontinuation, at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

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

All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

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

Investigators are not obligated to actively seek AEs or SAEs in former study 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. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

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.

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

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 5 half-lives after 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

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

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

Any pregnancy that occurs in a female partner of a male study 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.

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).

9.2.7 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

9.2.8 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

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report. Investigators must confirm the laboratory test results for participant's eligibility.

Results of clinical laboratory tests performed as part of screening must be available prior to dosing.

9.4.2 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics

Pharmacokinetics of Baraclude will be derived from plasma concentration versus time. The pharmacokinetic parameters to be assessed include:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
Ctrough	Trough observed plasma (predose) concentration
C24	Observed plasma concentration at 24 hours postdose
AUC(TAU)	Area under the concentration-time curve in one dosing interval
CLT/F	Apparent total body clearance

Table 9.5-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood collection and processing will be provided to the site in the procedure manual.

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.

Table 9.5-1: Pharmacokinetic Sampling Schedule for AI463528

Study Day of Sample Collection	Event	Time (Relative To Baraclude Dose) Hour: Min
1	predose	00:00
1	0.25	00:15
1	0.5	00:30
1	1.0	01:00
1	1.5	01:30
1	2	02:00
1	4	4:00
1	6	6:00
1	8	8:00
1	12	12:00
2	24	24:00

The plasma will be analyzed for Baraclude by a validated assay.

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

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

9.6 Pharmacodynamics

Not applicable.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Not applicable.

9.8.1 Additional Research Collection

This protocol will not include sample collection and/or residual sample storage for additional research (AR).

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

This is an estimation study. A sample size of approximately 8 participants will provide two-sided 95% confidence interval half-widths of 1.12, 8.93, and 136.63, respectively, for Cmax (ng/mL), AUC(TAU) (ng*h/mL), and CLT/F (mL/min) based on 80% coverage probability and historic standard deviations. These calculations are based on one-sample t-tests using historic standard deviations of 1.13, 9.03, and 138.1, respectively, for Cmax, AUC(TAU), and CLT/F, based on population PK modeling from participants with HBV following 14 days of oral 0.5 mg Baraclude

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Participants	All participants who sign informed consent
Treated Participants	All participants who take at least 1 dose of study treatment.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary endpoint.

10.3.1 Efficacy Analyses

Not applicable.

10.3.2 Safety Analyses

Not applicable.

10.3.3 Pharmacokinetic Analyses

Individual pharmacokinetic parameter values will be derived from plasma concentration versus time using non-compartmental methods. Values will be summarized with univariate statistics (n, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, maximum). Parameters will include: Cmax, Ctrough, C24, Tmax, AUC(TAU), and CLT/F.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen

Term	Definition
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450

Term	Definition
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
FSH	follicle stimulating hormone
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases

Term	Definition
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
mg	milligram
Mg^{++}	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight

Term	Definition
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
t	temperature

Term	Definition
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity

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

REGULATORY AND ETHICAL CONSIDERATIONS

GUIDELINES FOR MEDICAL AND HEALTH RESEARCH

This study will be conducted in accordance with:

- Ethical Guidelines for Medical and Health Research Involving Human Subjects
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

Revise the informed consent 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 or the participant's legally acceptable representative or legal guardian, 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 subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- 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)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to

Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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

ADVERSE EVENTS

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (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 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; 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.)

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 days days/weeks after the end of study treatment, plus 30 days

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

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

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 5 days after the end of treatment plus an additional 90 days.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 5 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 5 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 5 days after the end of treatment plus an additional 90 days.

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 the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

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

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

Criteria for Severity of Psychoactive Substance Dependence:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

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