Preflight Summary Report for: ai463528-csr-app-16-1-9-statplan-v1-Redacted_Redacted.pdf

Profile: Convert to PDF/A-1b (Processed pages 1 to 16)

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Fixups

- Prepare annotations for PDF/A-1 (64 objects)
- Convert to PDF/A-1b (2 objects)
- Force blend color space to sRGB (16 objects)
- Remove document structure compression (2 objects)
- Compress all uncompressed objects using lossless ZIP compression (1 object)
- Recompress LZW as ZIP (1 object)
- Fix font encoding (CIDSet) (10 objects)
- Insert CMap for CID fonts (10 objects)
- Remove unnecessary transparency groups (16 objects)
- Repair invalid bookmark hierarchies (1 object)

Results (Summary)

✔ **No problems found**

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STATISTICAL ANALYSIS PLAN
FOR CSR

A CLINICAL STUDY TO EVALUATE THE STEADY STATE PHARMACOKINETICS OF BARACLUDE IN PARTICIPANTS WITH HEPATITIS B VIRUS INFECTION

PROTOCOL AI463528

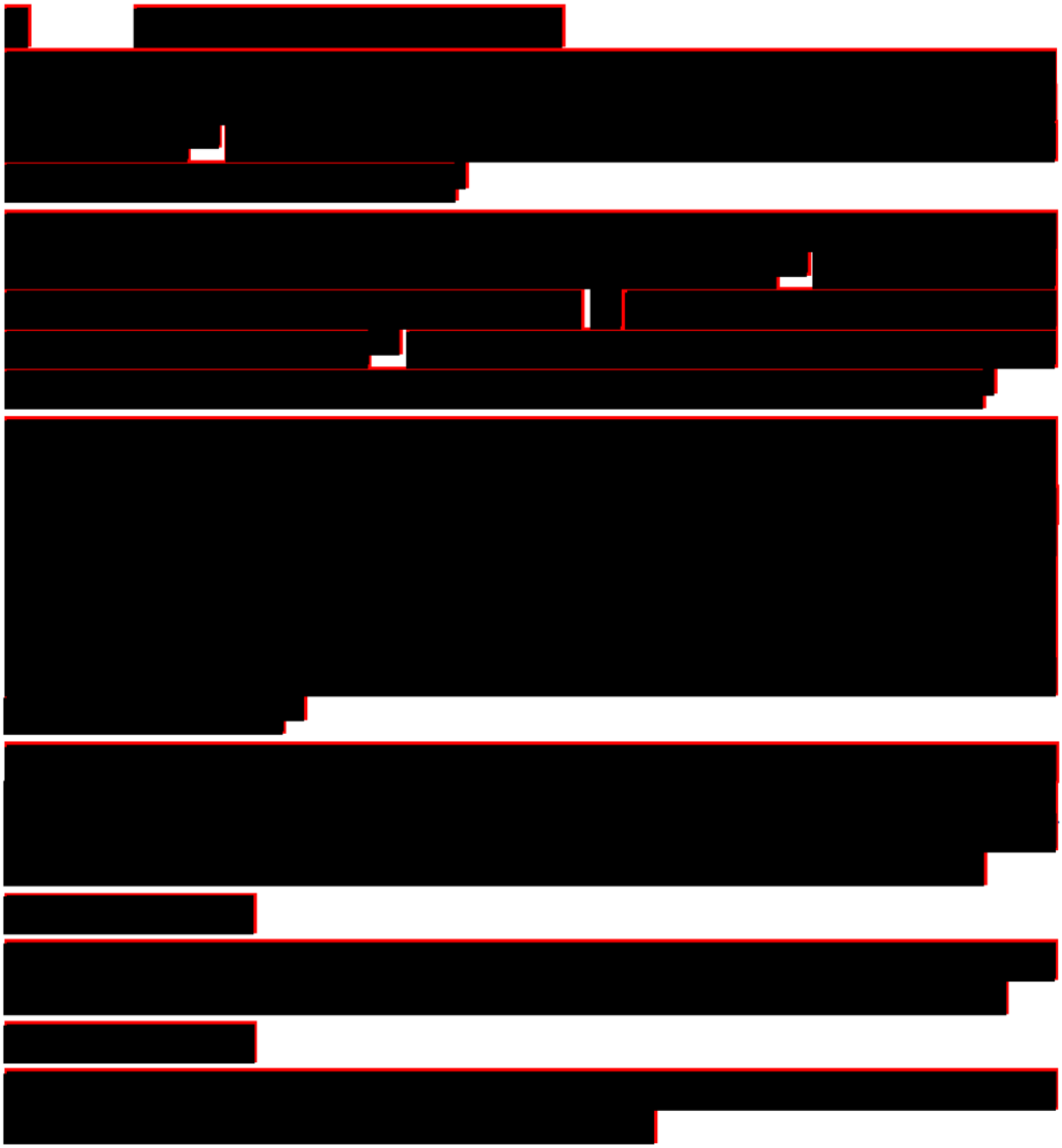
VERSION 1.0

REVISION HISTORY

Revision	Date	Revised By	Changes Made -- Reasons for the Change
1.0	16JAN2018	Eric Wu, Alexandra Thiry	Original issue

TABLE OF CONTENTS

LIST OF TABLES



2. STUDY DESCRIPTION

2.1 Study 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. Eligible participants include those that are taking 0.5 mg daily Baraclude for a minimum of 10 consecutive days prior to study enrollment.

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 4.3-2. 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 as well as up to 3 weeks for the screening period.

Participants are asked to take Baraclude once daily at the same time in the day (e.g., 9:00AM) for10 days during screening before entering the clinical site.

The study design schematic is presented in Table 2.1-1.

Table 2.1-1: 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 PK analysis. Participants will be closely monitored for adverse events throughout the study.

2.2 Treatment Assignment

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

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

The analysis plan is based on the study protocol dated 27 March 2017. There is no protocol amendment since then.

2.5 Data Monitoring Committee

Not applicable.

3. OBJECTIVES

3.1 Primary

The primary objective is to evaluate the steady state of Baraclude pharmacokinetics in HBV-infected participants.

3.2 Secondary

Not applicable.

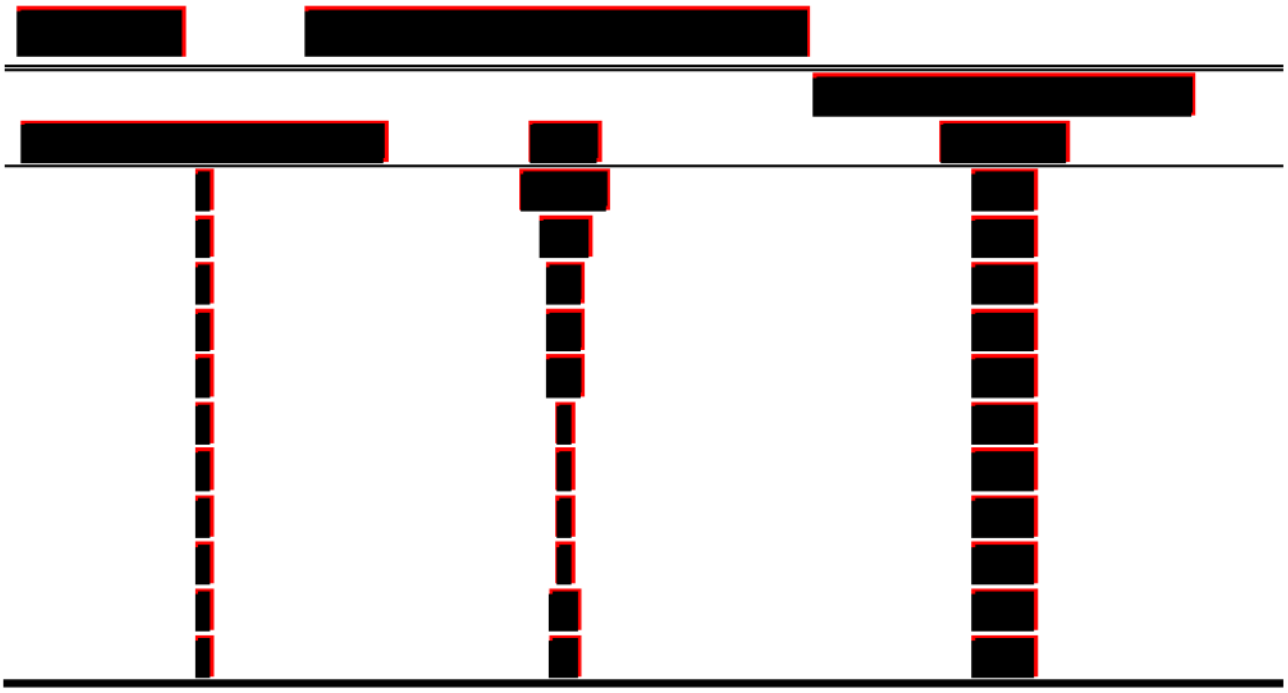
4. ENDPOINTS

4.1 Efficacy Endpoints

Not applicable.

4.2 Safety Endpoints

Not applicable.



5. SAMPLE SIZE AND POWER

This is an estimation study. A sample size of approximately 8 participants will provide two-sided 95% confidence interval (CI) half-widths of 1.12, 8.93, and 136.63, respectively, for C_{max} (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 C_{max}, AUC(TAU), and CLT/F, based on population PK modeling from participants with HBV following 14 days of oral 0.5 mg Baraclude.

6. STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The study will have 3 study periods:

- **Screening period** begins at the first visit and ends before the first dose of Baraclude administered as study drug (Day 1) in the clinic;
- **Treatment period** begins on the first dose of Baraclude administered as study drug (Day 1) and ends on the last dose of Baraclude administered as study drug in the clinic.
- **Follow-up period** begins after the last dose of Baraclude administered as study drug (Day 1) in the clinic until the last visit.

6.2 Treatment Regimens

The treatment regimen is described in Section 2.1. Participants will take a single oral dose of Baraclude 0.5 mg on Day 1 at the clinic.

6.3 Populations for Analyses

The following analysis populations are defined for this study:

- Enrolled participants: Participants who signed an informed consent form. This cohort will be primarily used for all listings, unless specified otherwise.
- Treated participants: Enrolled participants who receive at least one dose of study treatment (Baraclude) administered on Day 1 at the clinic. This cohort will be used to summarize demographics and safety.
- PK participants: Treated participants who have available PK concentration-time data. This cohort will be used for all PK listings.
- Evaluable PK participants: PK participants who have adequate PK profile (see Section 8.1.4). This cohort will be used to summarize PK concentrations and PK parameters.

7. STATISTICAL ANALYSES

SAS version 9.3 or higher will be used for statistical analyses and output (i.e., tables, listings, and graphs).

7.1 General Methods

Listings display all data regardless of study period by participant and visit (if applicable). Continuous variables will be summarized using univariate statistics, i.e., number of participants, mean, standard deviation (SD), median, minimum and maximum. Geometric mean and coefficient of variation (%CV) will also be presented for continuous plasma PK parameters. Categorical variables will be summarized using counts and percentages.

Where appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first dose of study medication.

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) in production. Non-study medications will be coded using the BMS World Health Organization (WHO) Drug Dictionary.

7.2 Study Conduct

Criteria for excluding participants in PK analyses are discussed in Section 8.1.4.

7.3 Study Population

7.3.1 Subject Disposition

Pre-treatment subject status will be summarized for enrolled participants for the following categories: enrolled; treated; not treated, including reasons for not treated (e.g., adverse event, death).

End of study subject status will be summarized for treated participants for the following categories: completing the study; not completing the study, including reasons not completing the study. End of study subject status will also be listed for treated participants.

7.3.2 Demographics and Other Baseline Characteristics

Demographic characteristics will be summarized as categorical variables (unless specified otherwise) for treated participants: age, both as continuous and categorical variables (< 65, ≥ 65 years); sex; race; country.

Demographic characteristics will be listed for enrolled participants.

7.4 Extent of Exposure

Baraclude study drug administration will be listed for treated participants.

Non-study medication will be listed for enrolled participants, and will include the medication category (i.e., previous, or post-treatment).

7.5 Efficacy Analyses

Not applicable.

7.6 Safety Analyses

7.6.1 Adverse Events

Investigators will determine the severity of AEs based on Common Terminology Criteria (CTC) Grades 1-5, and determine the relationship of AEs to study therapy (related, not related).

All AEs, including SAEs, non-SAEs, and deaths will be listed for enrolled participants.

Deaths will be identified from two sources of information:

- Subject status: discontinuation reason of death;
- AE/SAE: MedDRA higher level, lower level or preferred term contains 'death'; SAE outcome of death; SAE category of death; non-missing death date; non-missing cause of death.

By database lock, it is expected that all deaths will have been reported as SAEs.

7.6.2 Clinical Laboratory Evaluations

Laboratory test results will be listed for enrolled participants in the international system of units (ie, SI units). Laboratory test results will be graded according to the most recent version of Division of AIDS (DAIDS), or WHO if the DAIDS toxicity grade is not available (e.g., BUN/urea; chloride).[11, 12]

7.6.3 Electrocardiograms

ECG parameters, including heart rate, PR interval, QRS width, QT interval, and QTc (Bazett's or Fridericia's), interpretation of findings (normal, abnormal), and finding will be listed for enrolled

participants. ECG parameters outside of the ranges specified in Table 7.6.3-1 below will be flagged.

Table 7.6.3-1: Out-of-Range ECGs

Parameter	Range (msec)
PR	Value > 210
QRS	Value > 120
QT	Value > 500
QTcF	Value > 450

7.6.4 Vital Signs

Vital sign measurements, including body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate, will be listed for enrolled participants.

7.7.2 Pharmacokinetic Parameters

The following Baraclude PK parameter values will be summarized as continuous variables: C_{max}, T_{max}, C_0, C_{24}, AUC(TAU), and CLT/F.

Baraclude PK parameter values will be listed, including any exclusions and reasons for exclusion in the statistical summary.

7.8 Biomarker Analyses

Not applicable.

8. CONVENTIONS

Conventions will be followed as per the following BMS documents, unless specified otherwise: Global Biometric Sciences General Requirements for Statistical Outputs;[13] Global Standard Table Reporting Requirements Specification; [14] Global Standard Listing Reporting Requirements Specification.[15]

8.1 Pharmacokinetic Data

8.1.1 Decimal Places for Univariate Statistics in Summaries

%CV will be reported as integers. For other statistics except for SDs, values of 100 or higher will be presented as integers, values of 10 - < 100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 and geometric means will be displayed to three decimal places. SDs will be reported to a precision of 1 decimal place more than the mean.

8.1.2 Handling of Non-Quantifiable Concentrations

For plasma concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) will be displayed as "< LLOQ" in the listings and will be treated as missing in summaries. For the purpose of calculating PK parameters, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

8.1.3 Treatment of Outliers

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire plasma concentration-time profiles for a participant may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

8.2 Other

Missing and partial non-study medication start and stop dates (including unknown and continuing) will be imputed according to BMS Non-Study Medication Domain Requirements Specification in place at the start of programming.[17] Imputed dates will be used to classify medications as previous, current, concomitant or post-treatment.

Missing and partial AE onset dates will be imputed according to the BMS Adverse Event Domain Requirements Specification in place at the start of programming.[18] Imputed dates will be used to classify AEs into study periods.

9. CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report (CSR). Refer to the Data Presentation Plan (DPP) for templates of tables, and listings.

All problems according to Preflight profile Convert to PDF/A-1b

[15] Global Standard Listing Reporting Requirements Specification. Bristol-Myers Squibb Company. Version 1.1. September 1, 2016.

[16] Clinical Pharmacology and Pharmacometrics PK Harmonization Document. Guidance for Analysis and Reporting of Pharmacokinetic Data in Clinical Studies. Bristol Myers Squibb Company. Version 3.0. December 2014.

[17] Non-Study Medication Domain Requirements Specification. Bristol Myers Squibb Company. Version 2.10.0. February 22, 2017.

[18] Adverse Event Domain Requirements Specification. Bristol-Myers Squibb Company. Version 2.4.0. July 25, 2016.