STATISTICAL ANALYSIS PLAN FOR

Official Title of Study:

OPEN LABEL, ADAPTIVE DESIGN, ASCENDING, MULTIPLE-DOSE STUDY TO

EVALUATE SAFETY AND EFFICACY OF BMS-986004 (ANTI-CD40L DAB) IN

ADULT SUBJECTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

NCT Number: NCT02273960

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STATISTICAL ANALYSIS PLAN FOR

CLINICAL PROTOCOL IM140103

OPEN LABEL, ADAPTIVE DESIGN, ASCENDING, MULTIPLE-DOSE STUDY TO EVALUATE SAFETY AND EFFICACY OF BMS-986004 (ANTI-CD40L DAB) IN ADULT SUBJECTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

VERSION 1.0

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Schedule of Analyses:

- Interim analysis may be performed repeatedly with accumulating data, perhaps without formal database lock, to provide an intermittent dose.

- Final CSR reports will be provided with formal database lock.

2   STUDY DESCRIPTION

2.1   Study Design

This is a Phase 1b/2, multicenter, open-label, MAD study to evaluate the safety, efficacy, dose response, and pharmacology (PK, target engagement and PD) of BMS-986004 administered every 2 weeks in subjects with ITP.

Figure 2.1-1:   Study Design Schematic
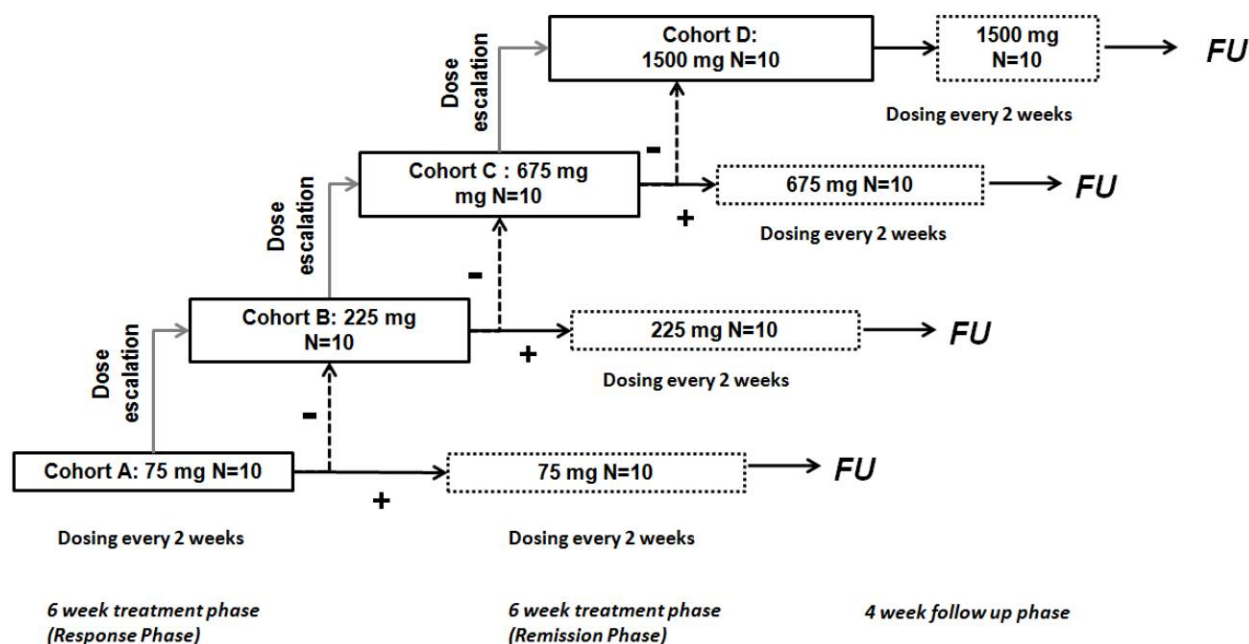
The study is divided into screening (3 weeks), response phase (6 weeks), remission phase (6 weeks) and follow up period (4 weeks). Forty subjects are treated in 4 dose panels, 75mg, 225mg, 675mg, and 1500mg, of 10 subjects each. BMS-986004 will be administered on day 1, 15, 29, 43, 57, 71, 85, a total of 7 doses as IV infusion. Four (4) doses will be administered during the Response Phase over a 6 week treatment period. The remaining 3 doses will be administered during the Remission Phase of the study over a 6 week treatment period. The study design schematic is presented in Figure 2.1-1.

Cohort of lower than 75mg or intermittent dose may be opened.

Intra-subject dose escalation

Subject may be dosed at a higher dose beginning from day 57 for the remainder of the study if clinically significant response has not been achieved at Day 43 and Day 50, and a favorable safety profile is observed.

Figure 2.1-2:   **Decision Rule on Intra-Subject Dose Escalation**
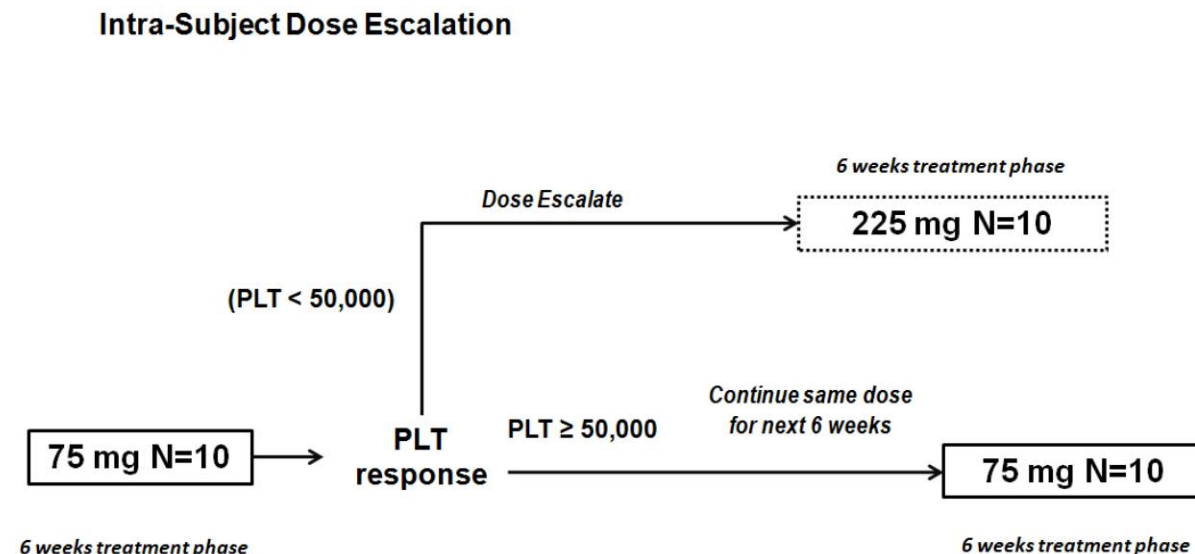
2.2 Treatment Assignment

Interactive Voice Response System (IVRS) will be used for assignment of subject number and cohort.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This analysis plan reflects all protocol amendments through Amendment 02, dated 31-Jul-2014.

3   OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to assess the overall safety and tolerability of multiple doses of BMS-986004, when administered in subjects with chronic ITP.

3.2 Secondary Objective

The secondary objectives are as follows.

- To evaluate efficacy of BMS-986004 in the treatment of thrombocytopenia in subjects with chronic ITP, as measured by platelet response/complete response (R/CR) and other clinical parameters.
- To establish BMS-986004 dose response, as measured by platelet count and other clinical parameters.

- To measure the target engagement of BMS-986004 following multiple IV doses
- To assess the effect of BMS-986004 on markers associated with the risk of thromboembolism (TE) in the multiple dose setting.
- To assess pharmacokinetics and immunogenicity of multiple doses of BMS-986004 in subjects with chronic ITP.

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4   ENDPOINTS

4.1 Efficacy Endpoints

The first secondary objective of efficacy will be measured by the following efficacy endpoint:

- Response Rate (RR): Response rate is defined as the proportion of subjects who are responders.
- Time to Response: It is defined as the time, in weeks, from the first dosing day until the criteria for PR or CR are first met, whichever occurs earlier. Non-responders will be censored on the date of their last platelet measurement.
- Duration of Response: Duration of response is defined as the time, in weeks, from the first day when the criteria are met for PR or CR, whichever occurs first, until the date of disease progression. Subjects who do not progress will be censored on the date of their last platelet measurement. It is defined for responders only.
- Time to Peak Response: It is defined as the time, in weeks, from the first dosing day until the largest platelet count is met. It is defined for responders only.

4.2 Safety Endpoints

Safety endpoints include incidence of AE at the highest grade, death as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, and physical examinations. Incidence of AEs is provided separately for overall AEs, serious AEs, and AEs leading to discontinuation.

4.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters of BMS-986004 will be derived from serum concentration versus time data by analyte and collection interval. Individual pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic analysis program using actual times.

Table 4.3-1:   **Commonly Used PK Parameters, Naming Conventions and Definitions**

Parameter	Definition
Cmax	Maximum observed serum concentration
AUC(TAU)	Area under the concentration time curve in one dosing interval
Ctrough	Trough observed concentration
CLT	Total body clearance
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

4.5 Immunogenicity Endpoints

Immunogenicity endpoint is proportion of subjects by subject ADA status, which includes positive at baseline, subject ADA positive (further divided into persistent positive, not persistent positive but with the last sample positive, and other positive), and subject ADA negative.

Below given are the definitions of various sample ADA status and afore mentioned subject ADA status. The definitions are current as of the time when this SAP was drafted and are consistent with the recommendations from internal immunogenicity council. In case any of the definitions be changed or new category added, the SAP won't be amended, and the data presentation plan (DPP) will be updated.

ADA Status of a Sample:
- Baseline ADA Positive Sample: ADA is detected in the sample before initiation of treatment
- ADA Positive Sample: After initiation of treatment, (1) an ADA positive sample in a subject who is baseline ADA negative, or (2) an ADA positive sample with ADA titer to be at least 9-fold or greater ($\geq$) than titer of a baseline ADA positive
- ADA Negative Sample: After initiation of treatment, no positive ADA sample

ADA Status of a Subject:
- Baseline ADA Positive Subject: A subject with baseline ADA positive sample
- ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment during the defined observation time period
    1. *Persistent Positive (PP):* ADA positive sample at 2 or more sequential time points, where the first and last ADA positive samples are at least 16 weeks apart
    2. *Not PP-Last Sample Positive:* Not persistent but ADA positive sample in the last sampling time point

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3. *Other Positive:* Not persistent positive but some ADA positive samples with the last sample being negative

- ADA Negative Subject**:** A subject with no ADA positive sample after the initiation of treatment

5   SAMPLE SIZE AND POWER

The number of subjects is not based on statistical power considerations.

6   STUDY PERIODS, TREATMENT GROUPS AND POPULATIONS FOR ANALYSES

6.1   Study Periods

The approximate duration of the study is 20 weeks (approximately 140 Days). This includes a 21 day screening period, a 12 week treatment period (6 weeks of response Phase and 6 weeks of remission phase) and a 1 month follow up period. The end of study will be defined as the date of the last visit of the last subject undergoing the study.

6.2   Treatment Groups

Treatment groups will be decided by the planned starting dose regardless of intra-subject dose escalation planned at day 57. Table 6.2-1 below indicates the planned treatment groups.

All summaries, except PK summary, will be provided by treatment group. For PK summary, it is current dose that is used to decide the dose group.

Table 6.2-1:   **Treatment Group**

Cohort	Treatment Group Label
A	BMS 75mg
B	BMS 225mg
C	BMS 675mg
D	BMS 1500mg

6.3   Populations for Analyses

- All Enrolled Subjects, defined as all subjects who signed an informed consent;

- All Treated Subjects, defined as all subjects who have received at least one dose of study treatment;

- Pharmacodynamic Population, defined as all subjects that receive any study medication and have PD biomarker data available,

- Pharmacokinetic Population, defined as all subjects who receive any study medication and have any available concentration-time data. Additionally, the evaluable PK Population is defined as subjects who have adequate PK profiles.

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

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations. S-Plus® version 8.1.1 or higher may also be used for graphical presentations. Exploratory analysis may be done with R or other software tools.

7.1 General Methods

All data recorded on case report forms will be listed by subject. Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Geometric mean and coefficient of variation (%CV) will also be presented for sample serum concentration-time data and PK parameters. Descriptive summaries for categorical variables will utilize counts and percentages.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA). Previous and concomitant medications will be coded using the WHO Drug Dictionary.

7.2 Study Conduct

Relevant deviations from the study protocol, protocol amendments and administrative changes will be documented and accounted for in presenting the data summaries, listings and descriptive statistical analyses. Deviations of protocol-specified inclusion and exclusion criteria will be listed. Any changes from planned protocol-specified analysis will be defined in the SAP and reported in the CSR.

7.3 Study Population

7.3.1 Subject Disposition

Subject disposition will be listed. Summary tables reflecting the number of subjects who are enrolled, who are treated, reasons for not entering treatment period and who completed the study will be presented for each treatment group and all.

7.3.2 Demographic Characteristics

Demographic characteristics such as gender, age, race and ethnicity will be listed for all treated subjects. Demographic characteristics will also be summarized for all treated subjects for each treatment group and all.

7.3.3 Physical Measurements

Physical measurements such as body weight, height and body mass index (BMI) will be listed for all treated subjects. Measurements will also be summarized at baseline by treatment group and overall for all treated subjects.

7.3.4 Medical History, Previous and Current Medications

Medical history will be listed for all treated subjects. Previous and current medication will be listed in ascending order of date for all treated subjects. In addition, rescue medications, if any, will be listed.

7.3.5   Study Procedure

Any conducted medical treatment procedures and utilized diagnostic procedures will be listed.

7.4 Extent of Exposure

Study drug administration and container number will be documented as per subject listings. No analysis regarding extent of exposure is planned. However, number of subjects having dose-escalation per treatment group will be provided along with efficacy summarizes (please see details in Section 7.5.4)

7.5 Efficacy

Efficacy results are assessed by platelet counts and bleeding SMOG scores obtained longitudinally through the study. The collection date and time are available in Table 7.10-1 (Both are collected at the same day).

7.5.1   Derivation of Efficacy Endpoints

Primary efficacy criteria and response category:
- Response (R) - platelet count $\geq 30,000/\text{mm}^3$ and at least 2-fold increase from the baseline count and absence of bleeding.
- Complete Response (CR) - platelet count $\geq 100,000/\text{mm}^3$ and absence of bleeding.
- No Response (NR) - platelet count < 30,000/mm3 or less than 2-fold increase of baseline platelet count or bleeding.
- Not Assessable (NA) - platelet count is missing or is excluded due to rescue medication.

Subject's best response is decided in the order of CR, R, NR, and NA.

Secondary efficacy criteria and response category:
- Clinically Significant Response - platelet count $\geq 50,000/\text{mm}^3$ with an increase of at least $20,000/\text{mm}^3$ from baseline and absence of bleeding.
- No Clinically Significant Response - platelet count < $50,000/\text{mm}^3$, or increase of $\leq 20,000/\text{mm}^3$ from baseline, or bleeding.
- Not Assessable (NA) - platelet count is missing or is excluded due to rescue medication.

Absence of bleeding:
Absence of bleeding is defined as SMOG scores being zero for all the three major domains (Skin, visible mucosae, and organs) with ITP-BAT on the same day when platelet count is assessed.

Platelet data exclusion and rescue medication flag:
Platelet counts collected within 4 weeks after any rescue medication, though still shown in listing of figures of raw data, will be excluded from summarizing platelet and deriving subject response. To facilitate the exclusion, rescue medication flag may be derived and included in some analysis datasets and listings if at least one subject takes rescue medication after the first dosing during the trial. Rescue medication flag is set to Y (Yes) within 4 weeks after the day any rescue medication is administered, i.e., between rescue medication day and rescue medication day + 27, inclusively. It will be set to N (No) when otherwise.

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7.5.2 Bleeding Score - SMOG

Bleeding, as measured by ITP-BAT SMOG, will be listed for all treated subjects. Due to the nature of the incremental assessment of ITP-BAT, evaluation period (start day and end day) will be provided. Start day of an assessment is the end day of the immediately previous assessment visit. Start day would be missing for the first bleeding assessment (screening visit).

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7.5.3 Platelet Count

Bleeding SMOG score, platelet count, platelet change from baseline, potentially rescue medication flag, and response category (each under primary and secondary efficacy criteria) at each study day will be listed for all treated subjects.

Platelet count and change from line will be summarized by treatment group for each study day. Percent of visits with platelet count $\geq 30,000/mm^3$, $50,000/mm^3$, and $100,000/mm^3$ will be listed for each subject and summarized for each treatment group.

Platelet count and its change from baseline may be explored by graphs and statistical models. Details are available in the section of exploratory biomarker analysis.

Exploratory analysis of platelet count is shown in section 0.

7.5.4 Response with primary efficacy criteria

The best response status over the entire study will be reported for all treated subjects with platelet at baseline, administered dose on day 1, and administered dose on day 57. For responders, treatment group, dose escalation status (Y/N), time to respond, time to peak response, and duration of response will be provided in a listing.

Response rates and number of subjects having dose escalated will be provided for each treatment group and all.

7.5.5 Response under secondary efficacy criteria

Overall response rates during the whole study will be provided for each treatment group and all.

7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by treatment ("as treated") and overall.

Adverse events (AEs) will be coded according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include (1) events occurring from the first dose date to 35 days (inclusive) after the last dose of BMS-986004 for subjects who are off study

treatment and (2) all events occurring from first dose date for subjects who are still on study medication.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.0) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and (1) post-baseline results up to 35 days (inclusive) after the last dose of BMS-986004 for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication.

7.6.1 Overall Adverse Events

AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

Summary:

Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT for each treatment group and arm.

Listing:

All recorded Adverse Events occurring in the pre-treatment, on-treatment, and post treatment period will be listed.

7.6.2 Deaths

Summary:

All deaths during the study within 35 days after the last dose of BMS-986004 will be summarized for cause of deaths by treatment group and arm.

Listing:

All recorded deaths during the study, including post-treatment follow-up period, and deaths that resulted from a process that began during the study, will be listed.

7.6.3 Serious Adverse Events

Summary:

Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT for each treatment group and arm.

Listing:

By-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.4   Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued".

Summary:

Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

Listing:

By-subject AEs leading to discontinuation listing will be provided.

7.6.5   Multiple Events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms in order to collapse adverse event records into unique records based on the preferred term. This data will be presented as the rate per 100 patient-years of exposure. This analysis will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The patient-years exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as

- Date of last dose of study treatment - date of first dose of study treatment +35 + 1 days, for subject who are off study treatment and were followed at least 35 days after last dose of study medication.

- Last known date alive - date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 35 days after last dose of study medication.

Summary:

The following summary tables will be provided for each arm:

Total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated in the arm.

For select AEs, if applicable:

Tables showing the number of subjects experiencing an AE once or multiple times in each arm

Listing:

Unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed.

7.6.6   Select Adverse Events

Select AEs under different categories, if present, will be summarized by the following table for each treatment group and arm:

- Overall summary of any select AEs by worst CTC grade presented by category/PT (any grade, grade 3-4, grade 5)

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The list of all select AE and the grouping category, if available, will be provided in a separate document, data presentation plan.

7.6.7 Clinical Laboratory Evaluations

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

Summary:

The number (%) of subjects with the following will be summarized by treatment group and arm, if appropriate, using the worst CTC grade on-treatment per subject for each gradable lab test.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline by treatment and study day

Listing:

A by-subject listing of these laboratory parameters will be provided

7.6.8 Thromboembolism (TE) Safety Biomarker

Thromboembolism safety biomarkers include Prothrombin time (PT), activated Partial thromboplastin time (aPTT). D-dimer, thrombin antithrombin (TAT), and Serum troponin I. Among the above safety biomarkers, PT and aPTT are collected during screening, and others are collected longitudinally on select study days.

TE safety biomarkers will be listed for all treated subjects in ascending order of collection day.

7.6.9 ECG

All of the available ECG parameter values from each subject will be provided in a listing. Abnormal findings of ECG will be presented separately.

7.6.10 Vital Signs

Vital signs parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be listed for all treated subjects.

7.6.11 Physical Examination Findings

All physical examination abnormal findings will be listed per subject and visit.

7.7 Pharmacokinetics

PK sampling date and time are shown below in Table 7.7-1 for convenience. On day 57, non-responders in each treatment group other than the 1500mg group will be dose-escalated to the starting dose of the next higher treatment group.

The Pharmacokinetic (PK) population will be used for all listings. Evaluable PK population will be used for summaries. PK parameters and Ctrough will be summarized for each group decided by current dose, and dose proportionality analysis will be provided by excluding subjects who have dose escalation on day 57.

Table 7.7-1:   **PK Sample Study Day and Time**

study day	dosing	PK Sampling
1	#1, at starting dose	0h, 2h, 24h, 72h, 168h
15	#2, at starting dose	0h
29	#3, at starting dose	0h
43	#4, at starting dose	0h, 168h
57	#5, Responder: at starting dose Non-Responder: at titration dose	0h, 2h
71	#6, at the same dose as Day 57	0h, 2h, 24h, 96h, 168h
85	#7, at the same dose as Day 57	0h, 336h, 672h

7.7.1   PK Parameters

All individual PK parameters will be listed for BMS-986004 including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameters by treatment and by study day. Geometric means and coefficients of variation will be presented for Cmax, AUC(TAU), CLT, AI_AUC, and AI_Cmax. Decimal place specifications for summary statistics are described in Section 7.11.

PK parameters will be summarized for day 1 and day 71 with the grouping decided by current dose - the planned dose on each of the two study days, as subjects are expected to have achieved steady state by day 71. Under this assumption, the PK parameters are considered to be related to the current dose, regardless of the previous doses. As such, 75mg dose group on day 71 consists of subjects dosed at 75mg only; 225mg dose group on day 71 consists of subjects from both non-responders of 75mg cohort and responders of 225mg cohort, all of whom will be dosed at 225mg; 675mg dose group on day 71 consists of subjects from both non-responders of 225mg cohort and responders of 675mg cohort; 1500mg dose group on day 71 consists all of the subjects from 1500mg cohort and also the non-responders from 675mg.

7.7.2   Ctrough Summary

Ctrough will be listed for all available data and summarized on day 15, 29, 43, 57, 71, and 85 for each group decided by previous dose.

7.7.3   Dose Proportionality

Dose proportionality will be provided separately for Cmax and AUC(TAU) on study day 1 and 71 using a power model. Particularly, subjects going through dose escalation will be removed from the proportionality analysis for day 71. With the expected response rate of between 20% - 50% for 75mg, 225mg and 675mg, there would still be enough subjects left for the proportional analysis on day 71 after responders are removed. All subjects of 1500mg cohort will be included. In case there is no subject (all of the subjects are non-responders), or there are very few subjects (e.g., less than 3 subjects) in both 75mg and 225mg groups, dose proportionality analysis will not be provided for day 71. Decision will be data driven. Analysis results on day 71 will be discussed in the CSR if available; otherwise results on day 1 will be discussed.

The power model was described by Gough et al,[1]

$$PK\ Parameter = A*Dose^{\beta}.$$

Parameter of the above model, β, will be estimated by the simple linear regression of the natural log of the PK Parameter on the natural log of Dose:

$$E[\log(PK\ Parameter)|\ Dose] = \alpha + \beta*\log(Dose).$$

For each PK parameter, the point estimate of slope β and its 90% CI will be provided. In addition, the estimated regression line will be overlaid on the individual points in the corresponding scatter plot (log-log scale).

A slope (β) equal to 1 would indicate perfect dose proportionality. However, as the study is neither optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality, these results should be interpreted with caution.

7.7.4 Other Analysis

Subject serum concentration-time profiles will be listed and summarized by treatment and nominal collection time for BMS-986004. Plot of individual serum concentration profiles over time will be provided. Overlay of individual serum concentration profiles over time will be provided by treatment. Plots of mean (+SD) serum concentration profiles versus time will be presented for analyte, and all treatments will be superimposed on the same plot. Plots of mean (+SD) serum concentration profiles versus time will also be presented for each treatment, and all analytes will be superimposed on the same plot.

7.9 Immunogenicity Analysis

<u>Summary</u>:

Number (%) of subjects will be reported for the following parameters based on Evaluable Subjects.

- Baseline ADA-positive
- ADA-positive
  – Persistent Positive (PP)

   – Not PP-Last Sample Positive

   – Other positive

- ADA-negative

Listing:

- A listing of all ADA assessments will be provided together with titer value, sample ADA status, subject ADA status and time-matched BMS-986004 concentration level.

- A separate listing of ADA assessments for subjects with at least one positive assay.

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7.11 Conventions

EmBARC (Enhanced Biometric Analysis & Reporting Capability) standard time windowing, imputation rules, and counting rules will be applied.

7.11.1   Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the

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standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

7.11.2 *Pharmacokinetic Summaries*

<u>In-text Tables</u>

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, 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 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

<u>Handling of Non-Quantifiable Concentrations</u>[2]

For the summaries of serum concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, 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.

Summary statistics for Ctrough concentrations, analyses of PD-concentrations and ECG-concentrations relationships will be calculated by imputing values less than LLOQ as ½ * LLOQ. This imputation is done for Ctrough concentrations because it is treated like a PK parameter; the imputation is not done for Day 1 pre-dose concentrations. Individual Ctrough listings will display these concentrations as "< LLOQ."

All available serum concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

<u>Treatment of Outliers</u>

Individual serum 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 serum concentration-time profiles for a subject 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.

<u>PK Exclusions</u>[2]

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 9.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, subjects may be excluded from the analysis if they missed doses, had diarrhea, or vomited at or before a time equal to twice the median Tmax for immediate-release products, or vomited at any time during sampling after the administration of modified-release formulations.

8   CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). It is assumed that a full CSR will be expected for the study IM140-103 at the writing of the SAP. If it is not the case, the SAP won't be updated. Details of the tables, listings, and figures to be prepared for the CSR will be included in a study-specific Data Presentation Plan (DPP).