Official Title of Study:

A PHASE 1, OPEN-LABEL STUDY OF ULOCUPLUMAB (BMS-936564) IN COMBINATION WITH LOW DOSE CYTARABINE IN SUBJECTS WITH ACUTE MYELOID LEUKEMIA

NCT Number: NCT02305563

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NEW or MODIFIED **STATISTICAL ANALYSIS PLAN** APPROVAL PAGE

Study-Specific SAP for CA212-016

A PHASE 1/2, RANDOMIZED OPEN-LABEL STUDY OF ULOCUPLUMAB (BMS-936564) IN COMBINATION WITH LOW DOSE CYTARABINE IN SUBJECTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA

Version 1.0

Prepared by:

Stephen Francis Statistician	[redacted]	Signature	Date

Approved by:

[redacted]

☐ Study-Specific SAP (NIR)	NIR Study Director	Signature	Date
	TA Head of GHEOR, GPV&E, or Local/Regional HEOR	Signature	Date
	GBS Lead, or GBS M&MA Lead (if applicable)	Signature	Date
☐ Core or Integrated SAP	GBS Lead	Signature	Date
	Medical Lead	Signature	Date
	GBS Head of Specialty or Oncology	Signature	Date
	Development Lead	Signature	Date
☐ Summary of Clinical Pharmacology	TA Head, CP&P	Signature	Date
	GBS Head of Specialty or Oncology	Signature	Date
☐ Early Phase Standard SAP	GBS Head of Specialty or Oncology	Signature	Date
	CFIG or Oncology Department Head	Signature	Date

***(For Early Phase Standard studies, if there is no Medical Lead, secure approval from the TA Head for Early Phase Standard Studies according to the functional area of the Study Director or his/her designee)*

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STATISTICAL ANALYSIS PLAN
FOR INTERIM AND FINAL ANALYSES
OF ESCALATION COHORT (PHASE 2)

A PHASE 1/2, RANDOMIZED OPEN-LABEL STUDY OF ULOCUPLUMAB (BMS-936564) IN COMBINATION WITH LOW DOSE CYTARABINE IN SUBJECTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA

VERSION # 1.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

[redacted]

Research Hypothesis:

The study has no formal research hypothesis to be statistically tested.

2 STUDY DESCRIPTION

2.1 Schedule of Analyses

Phase 1 (escalation cohort) has previously been analyzed; the original SAP is attached as an appendix to this document. This SAP applies similar methodology to Phase 2 (expansion cohort), the following analyses of which are planned:

Table 1: Planned Analyses of Expansion Cohort

Meeting/Format	Timing	Purpose
DMC Interim #1	When the first 6 subjects in the ulocuplumab 1000mg arm have had opportunity for 28 days of follow-up	Review of all available safety data, especially pertaining to the ulocuplumab 1000mg dose; results will be available for review by BMS also
DMC Interim #2	When around 60 subjects (20 per treatment arm) have completed 2 months of treatment and follow-up	See DMC Charter for additional details; results will be available for review by BMS also
DMC Interim #3 (SAE only)	About 12 months after interim #2	See DMC Charter for additional details
Final analysis	After all patients have had opportunity for 6 months of follow-up	For final report (CSR)
DMC final meeting	When 100% of subjects have completed or discontinued from all study drugs	Review all safety data for the proposed treatment regimen and provide insight for potential future trials
Study completion analysis	At completion of study (subject follow-up complete)	Review mature OS data

2.2 Study Design

A total number of 6 (Phase 1) plus up to approximately 120 (Phase 2), i.e. 126 subjects overall, will be treated in this study. The entire study is expected to last approximately 7 years, with the addition of the expansion cohort and overall survival (OS) follow up.

Cohorts

Phase 1: an open-label escalation cohort of 6 subjects with AML to assess the safety and tolerability of ulocuplumab.

Phase 2: an exploratory, non-comparative open-label expansion cohort of up to approximately an additional 120 AML subjects, randomized in a 1:1:1 manner to the following treatment arms:

1) ulocuplumab 800 mg in combination with LDAC 20 mg BID;
2) ulocuplumab 1000 mg in combination with LDAC 20 mg BID;
3) LDAC 20 mg BID alone.

Randomization will be suspended in the ulocuplumab 1000 mg + LDAC arm while safety data from the first 6 subjects in this arm are evaluated for DLTs (as part of DMC Interim #1). DLTs and all other toxicities are defined and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03). DLTs are defined based upon events considered to be related to ulocuplumab in combination with LDAC and that occurred during the first cycle of drug administration (28 days). Randomization to the

ulocuplumab 1000 mg + LDAC arm will resume if ≤ 33% of subjects experience a DLT. If > 33% of subjects are observed with DLTs, this treatment arm will not accrue additional subjects.

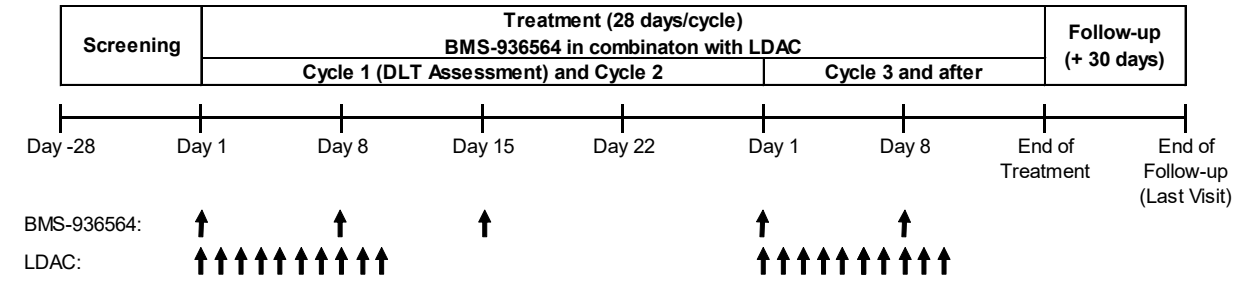
Study Periods

The study consists of the following 3 periods:

- Screening: the 28 days following initiation of screening assessments and before administration of the first dose of any study drug, during which subjects are evaluated for study eligibility.
- Treatment: subjects will receive LDAC on Days 1-10 of each 28-day cycle. In addition, subjects randomized to arms 1 and 2 will be administered ulocuplumab on Days 1 and 15 (also on Day 8, in cycles 1-2). Subjects who are tolerating study treatment, clinically stable and not progressing rapidly at the end of each cycle may continue with additional cycles until disease progression, development of unacceptable toxicity, intercurrent illness preventing treatment, or patient request or investigator decision to stop treatment. Delay of subsequent cycles for recovery from myelosuppression (or other AE) is allowed at investigator discretion.
    - Note: for the LDAC alone arm, ulocuplumab 800 mg may be added on Days 1 and 8 (also on Day 15, in cycles 1-2) if a subject does not achieve CR or CRi confirmed by blast count reduction after 4 treatment cycles or if they relapse after achieving complete remission.
- Follow-up: a follow-up visit will be completed 30 (± 7) days from the last dose of study therapy. Subjects will continue to be followed every 3 months for ongoing drug-related AEs until they have resolved, returned to baseline or are deemed irreversible, or until loss to follow-up or withdrawal of study consent. Subjects will also be followed every 3 months for OS for up to two years, until death, loss to follow-up or withdrawal of study consent.

The study design schematic is presented in Figure 1. Further details of the study design may be found in Section 3.1 of the Protocol.

Figure 1: Study Design Schematic



2.3 Treatment Assignment

After informed consent has been obtained and the subject's initial eligibility is established, the subject is assigned a subject number in IWRS. Following completion of all screening evaluations, site personnel will make a call to the IWRS, which will randomly assign Phase 2 subjects in a 1:1:1 manner to one of the 3 treatment arms (as described in Section 2.2). Randomization to the ulocuplumab 1000 mg + LDAC arm will be suspended while the safety of the first 6 subjects on this dose is assessed (see Section 2.2). Note that randomization will continue in the other 2 arms during this review. (Therefore, expected total numbers randomized are approximate.)

2.4 Blinding and Unblinding

The study is open-label.

Unblinded reports of interim data will be available to the DMC, without the use of fully- or partially-blinded treatment codes. Treatment codes will be provided by the BMS randomization coordinator to the reporting statistician after the database lock for the DMC analyses. Interim results for this exploratory study (for which there will be no inferential testing between treatment groups) will be available for review by a limited number of BMS personnel for planning purposes.Protocol Amendments

There are currently 7 amendments. The history of protocol amendments is summarized in the table below.

Table 2: Protocol Amendments

Amendment	Date	Main changes
1	24 Oct 2014	Clarifications in response to the PMDA review for Clinical Trial Notification
2	7 May 2015	Removal of restriction on AML (newly diagnosed, elderly); modification of prior therapy-related criteria and hepatitis B and C infection criteria
3	2 Nov 2016	Addition of randomized expansion cohort, with primary objective to assess preliminary efficacy; clarification of Phase 2 secondary objectives (safety and tolerability, overall remission [OR], CR/CRi, duration of remission [DoR], OS); added exploratory objectives (receptor occupancy [RO] and biomarkers)
4 (Brazil only)	19 Jan 2017	Clarification of post-study access to therapy in Brazil
5	10 Feb 2017	Addition of central laboratory cytogenetic testing; clarification of dosing and study assessment details
6	29 Mar 2017	Clarification of Phase 2 design (as exploratory, non-comparative; primary analysis to be conducted after all patients had opportunity for 6 months of follow-up; clarified that DoR will be censored on the date of last relapse-related assessment prior to the initiation of alternative anti-cancer therapy); increased local laboratory window allowances for hematology, chemistry and urinalysis to 72 hours; clarification of dose modifications and dose delays; clarification of study design; addition of whole exome sequencing to bone marrow and peripheral blood biomarker testing; added ECG, biomarker, cytogenetic and molecular analysis sections.
7	27 Jul 2017	Revision of exclusion criteria to specify allogeneic transplants in patients who received prior hematopoietic stem cell transplantation; clarification of hematology sampling schedule during cycles 1 and 2; revision of peripheral

		blood and serum/plasma collection criteria during end-of-study treatment and follow-up assessments.

3 OBJECTIVES

See original SAP in the appendix for Phase 1 (escalation cohort) objectives. Below are shown the Phase 2 (escalation cohort) objectives.

3.1 Primary

- To estimate preliminary efficacy in terms of complete remission (CR/CRi = CR + CRi) in subjects treated at two different dose levels of ulocuplumab, 800 mg and 1000 mg, in combination with LDAC

3.2 Secondary

- To characterize the immunogenicity of ulocuplumab
- To characterize the PK profiles of ulocuplumab in combination with LDAC
- To evaluate the effects of ulocuplumab on ECG intervals, including QTc intervals

- To assess OS in subjects treated with ulocuplumab 800 mg or 1000 mg in combination with LDAC
- To assess the safety and tolerability of ulocuplumab in subjects with AML treated with ulocuplumab at two different dose levels 800 mg and 1000 mg in combination with LDAC
- To assess rates of OR (= PR + CR + CRi) as well as duration of complete remission (CR/CRi) in subjects treated with ulocuplumab at two different dose levels 800 mg and 1000 mg in combination with LDAC
- To assess efficacy (in terms of rates of CR/CRi and OR and DoR, respectively, in subjects treated with LDAC alone, to compare with historical controls of LDAC in the same patient population. Overall survival will also be assessed in this group.

4 ENDPOINTS

This section summarizes Phase 2 (expansion cohort) efficacy, safety and other endpoints.

4.1 Efficacy Endpoints

4.1.1 Primary Endpoint

- Rate of complete remission (CR/CRi), prior to the initiation of any alternative therapy (including any subsequent ulocuplumab 800 mg for subjects in the LDAC alone arm). Response will be assessed by the investigator in accordance with the 2003 International Working Group (IWG) response criteria. The primary analysis will be conducted after all patients have had opportunity for 6 months of follow-up.

4.1.2 Secondary Endpoints

- Rate of OR (= PR + CR + CRi)
- DoR: the time from the date of first documented CR/CRi to the date of death or relapse. For subjects who remain alive and have not relapsed following remission, DoR will be censored on the date of last relapse-related assessment prior to the initiation of alternative anti-cancer therapy.
- OS: the time between the first date of treatment and the date of death due to any cause. A subject who has not died will be censored at the last known alive date.

4.2 Secondary Safety Endpoints

Safety and tolerability will be assessed through AEs, AEs leading to discontinuation, SAEs, deaths and laboratory abnormalities in combination therapy during the treatment period plus 30 days of follow-up. AEs will be graded according to NCI CTCAE v4.03.

Triplicate measurements of each serial ECG will be used to obtain an average value for each time point. Baseline will be defined as the time point prior to dosing on the first day of Cycle 1. All available non-missing values of ECG parameters should be used in the analyses. However:

- if QTcF is missing and RR in seconds is available, then QTcF will be calculated as QTcF = QT / RR(1/3);
- if both QTcF and RR in seconds are missing, then QTcF will be calculated as QTcF = QT / (60 / HR)(1/3).

The primary ECG endpoint is ΔQTcF, the change from baseline in QTcF, the QT interval normalized using Fridericia's heart rate correction. Other endpoints include QTcF, QT, QRS, PR, HR (heart rate), and QTcB as well as ΔQT, ΔQRS, ΔPR, ΔHR (heart rate), ΔQTcB, the associated changes from baseline. (Note: QTcB is the QT interval normalized using Bazett's heart rate correction.)

4.3 Secondary Pharmacokinetic Endpoints

The following pharmacokinetic (PK) parameters will be determined, whenever data permit:

Cmax	Maximum observed serum concentration
Ctrough	Trough observed serum concentration
Tmax	Time of maximum observed ulocuplumab serum concentration

AUC(0-T)	Area under the ulocuplumab concentration-time curve from time zero to the last quantifiable concentration (calculated by log- and linear-trapezoidal summation)
AUC(TAU)	Area under the ulocuplumab concentration-time curve in one dosing interval
AUC(INF)	Area under the ulocuplumab concentration-time curve from time zero to infinity (calculated by summing AUC(0-T) and the extrapolated area, computed by the quotient $C_{last}/\lambda z$)
T-HALF	Elimination half-life, determined as $0.693/\lambda z$
CLT	Total body clearance of ulocuplumab (calculated by dividing the total dose of ulocuplumab by its corresponding AUC(INF) value)
Vss	Volume of distribution at steady state

AUC from the time of dosing extrapolated to infinity (AUC[INF]) after first dosing, CLT, Vss and T-HALF will be calculated when feasible. Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

4.4 Secondary Immunogenicity Endpoints

Immunogenicity is measured by the incidence of anti-drug antibodies for ulocuplumab. Based on the recommendation from BMS Immunogenicity Council, White Paper on Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations by Shankar et al,1 and the FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products,2 the following definitions of ADA status will be applied**:**

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment
- ADA-positive sample: after initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least *4*-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline

[redacted]

5 SAMPLE SIZE AND POWER

The size of the study is not based on testing a formal statistical hypothesis. For Phase 2 (expansion cohort), a sample size of 40 subjects per treatment group will allow estimation of the response rate with the following degree of precision, where response is defined by complete remission (CR/CRi). A response rate of 0.6 will be estimated with a 95% exact confidence interval (CI) of 0.43 - 0.75. If the response rate is 0.45, then the associated 95% CI will be 0.29 - 0.62.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Within each phase, this study consists of three analysis periods: pre-treatment, on-treatment, and post-treatment.

- The pre-treatment period extends from the time of signing the informed consent form to prior to the first dose of study medication.
- The on-treatment period starts at the time of the first dose of study medication and ends 30 days following the last day of dosing (if a subject discontinues study medication).
- The post-treatment period begins after 30 days following the last day of dosing.

6.2 Treatment Regimens

Unless otherwise specified, analyses will be performed by Phase 2 treatment arm:

1) ulocuplumab 800 mg in combination with LDAC 20 mg BID;
2) ulocuplumab 1000 mg in combination with LDAC 20 mg BID;
3) LDAC 20 mg BID alone.

Demographic and baseline characteristics, as well as (Phase 2) efficacy, will be summarized (in all randomized subjects) by treatment arm as randomized (per IWRS). Safety and exposure will be summarized (in all treated subjects) by treatment arm as treated. (In general, 'as treated' will be the same as 'as randomized'. However, if a subject received an incorrect drug for the entire period of treatment, the subject will be summarized according to the incorrect drug that the subject actually received.)

6.3 Populations for Analyses

The following populations will be defined:

- *All Enrolled Subjects:* All subjects who signed an informed consent form and were registered into the IWRS. Subject disposition will be tabulated using this dataset.
- *All Randomized Subjects* (expansion cohort only): All subjects who signed an informed consent form and were randomized to either ulocuplumab 800 mg or 1000 mg in combination with LDAC or to LDAC alone. Demographic and baseline characteristics, as well as Phase 2 efficacy, will be summarized in all randomized subjects.
- *Response-evaluable subjects* (around 60 subjects at time of Interim Meeting #1): All randomized subjects who have opportunity to complete at least 2 cycles of treatment and

follow-up during the expansion phase. This will be the basis of some Phase 2 efficacy analyses in DMC Interim #2.

- *All Treated Subjects:* All subjects who received at least one dose of any study medication (ulocuplumab in the combination arm and LDAC in the LDAC only arm). Safety and exposure (as well as Phase 1 efficacy), will be summarized in all treated subjects.
- *PK Subjects:* All treated subjects who received at least one dose of ulocuplumab and have evaluable PK data.
- *Immunogenicity Subjects:* All subjects treated with ulocuplumab who have baseline and at least one post-baseline immunogenicity assessment.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise specified, the following are analyses of the expansion cohort, by treatment group, and will be produced for both DMC interim #2 and final analyses. A subset of these analyses will support DMC interim #1 and DMC interim #3 (SAE); further details will be given in the DPP and DMC Charter.

In general, continuous variables will be summarized using descriptive statistics, i.e. mean, standard deviation, median, minimum and maximum values. Geometric mean and coefficient of variation will also be presented for sample serum concentration-time data and PK parameters. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100.

7.2 Study Conduct

7.2.1 Accrual

- Accrual summary by country and site (numbers enrolled, randomized).
- Accrual listing (with informed consent date, country, investigational site, randomization date)

7.2.2 Relevant Protocol Deviations

The following relevant deviations will be summarized:

- Subject not AML (de novo or secondary) with blasts ≥ 20%;
- ECOG > 3;
- screening WBC ≥ 100,000 mL;
- screening creatinine > 2 mg/dL;
- screening AST or ALT > 3 x ULN;
- screening total bilirubin > 2 mg/dL;
- prior surgery within 4 weeks of first ulocuplumab dose;
- prior new investigational therapy within 4 weeks prior to first ulocuplumab dose;
- prior AML therapy (other than hydroxurea);
- concomitant use of AML systemic therapy;
- on-study use of new investigational therapy.

- Relevant deviations summary
- Relevant deviations listing

7.3 Study Population

7.3.1 Subject Disposition

The following will be provided:

- Pre-randomized subject status summary (with number of subjects enrolled, randomized, not randomized - with reason)
- Pre-treated subject status listing (with randomization date, treated, reason not treated)
- End of treatment period subject status summary (numbers continuing/not continuing in treatment period - with reason, continuing/not continuing in study - with reason)

  For LDAC-alone subjects who enter a period of ulocuplumab treatment, the status of this added treatment will similarly be summarized:

  - ♦ End of added ulocuplumab period subject status summary
- End of treatment period subject status listing (continuing in treatment period, reason not continuing, continuing in study)
- End of follow-up subject status summary (numbers continuing/not continuing to be followed - with reason)
- End of follow-up subject status listing (continuing to be followed, not continuing - with reason)

7.3.2 Demographics and Other Baseline Characteristics

7.3.2.1 Demographics and Baseline Disease Characteristics

The following will be provided:

- Demographic characteristics summary (age [descriptive statistics], age categorization [<70, >=70], gender, race)
- Disease characteristics summary (ECOG performance status, Hematopoietic Cell Transplant-comorbidity index [HCT-CI: 0-4, 5-9, 15-19, 20-24, 25+])

7.3.2.2 Prior Cancer Therapy

- Prior radiotherapy summary (yes/no)
- Prior systemic cancer therapy summary (yes/no, number of regimens)
- Prior cancer therapy listing

7.3.2.3 Physical Measurements

- Physical measurements summary (descriptive statistics for body weight, height and body mass index)
- Physical measurements listing (body weight, height, body mass index)

7.4 Extent of Exposure

7.4.1 Study Therapy

Duration of therapy (in days) is defined as date of last dose of therapy - date of first dose + 1. Cumulative dose (mg) is the sum of all actual doses that a subject received. Relative dose intensity (%) is defined as dose intensity / planned dose intensity x 100, where dose intensity (mg/day) = cumulative dose/ duration on assigned dose level in days.

Duration on assigned dose level will be calculated as follows:

- TD= last dose date of Ulocuplumab- first dose date of Ulocuplumab +1
- If last non-zero dose is at Cycle 1 or Cycle 2:
  1) if the last dose is first scheduled dose of that cycle, then duration on assigned dose level = TD+7;
  2) If last dose is second scheduled dose of that cycle, then duration on assigned dose level = TD+7;
  3) If last dose is third (last) scheduled dose of that cycle, then duration on assigned dose level = TD+14.
- If last non-zero dose is at Cycle 3 or later:
  1) if the last dose is first scheduled dose of that cycle, time on treatment = TD+7;
  2) If last dose is second scheduled dose of that cycle, then time on treatment = TD+21.

Planned dose intensity will be calculated as follows:

- Cycle 1 or Cycle 2: Planned Dose Intensity = (Assigned Dose * 3) / 28 days
- Cycle 3 or later Planned Dose Intensity = (Assigned Dose * 2) / 28 days
-

The following will be provided:

- Duration of ulocuplumab summary (1-28, 29-56, 57-84, 85-168, >=169; median, min-max)
- Duration of LDAC summary (1-28, 29-56, 57-84, 85-168, >=169; median, min-max)
- Number of ulocuplumab infusions summary (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, >10)
- Cumulative dose summary (descriptive statistics [mg])
- Relative dose intensity summary (<60%; 60-< 80%; 80-<90%; 90-<100%; >=100%)
- Extent of exposure listing (with duration of therapy, cumulative dose, relative dose intensity)

7.4.2 Modifications of Study Therapy

- Dose change summary for ulocuplumab (numbers with dose modification, dose interruption - with reason, dose delay - with reason, dose omission, dose discontinuation)

Dose change summary for LDAC?

- Dose change listing

7.4.3 Concomitant Medications

Concomitant medications (taken up to 30 days following the last dose of study therapy) will be tabulated and listed.

- Non-study medications summary (number of subjects by WHO anatomic class, therapeutic class and generic name)
- Non-study medications listing

7.5 Efficacy

7.5.1 Complete Remission Rate and Other Response Endpoints

The rate of subjects with complete remission (CR/CRi) will be summarized by a binomial response rate, and corresponding two-sided 95% exact CI using the Clopper and Pearson method. This will be based on best overall response prior to the initiation of any alternative therapy (including any subsequent ulocuplumab 800 mg for subjects in the LDAC alone arm). The rate will be based on all randomized subjects, except at DMC Interim #2, when the calculation will be based on response-evaluable subjects. The rate of OR (= CR/CRi/PR) will similarly be summarized.

- Best response and remission rates summary (best response categorization [CR, CRi, PR, TF]; rates of complete and overall remission)
- Best response listing (with overall response by visit, best response)
- Bone marrow blast assessments plot (% change from baseline)
- Bone marrow blast assessments listing (with bone marrow blast [%], % change from baseline, best reduction, presentation of Auer rods by visit)
- Extramedullary disease listing (disease presence and disease site)
- RBC transfusion listing (type of transfusion)

7.5.2 Overall Survival

OS will be estimated using Kaplan Meier (KM) methodology. Median OS will be estimated, along with two-sided 95% CIs using the Brookmeyer and Crowley method, considering a log-log transformation.

- KM plot of OS

7.5.3 Duration of Remission

For subjects who achieve CR or CRi, DoR will be estimated in the same way as OS.

- KM plot of DoR

7.5.4 Subsequent Therapy

- Summary of subsequent cancer therapy (number of subjects with any, radiotherapy, surgery, systemic therapy)
- Listing of subsequent cancer therapy

7.6 Safety

AEs will be coded according to the most current version of MedDRA and be graded using the NCI CTCAE version 4.03. Drug-related AEs are events with a relationship to study drug of 'Related' (as recorded on the CRF). If the relationship to study drug is missing, the AE will be considered drug-related.

Summaries of AEs will be based on on-treatment events, i.e. those occurring from the first dose date to up to 30 days (inclusive) after the last dose of study medication for subjects who are off-

treatment. Tables of AEs by CTC grade will be 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.

7.6.1 Deaths

The following will be provided:

- Death summary (all deaths, deaths up to 30 days of last dose: number of subjects, with primary reason)
- Listing of deaths (in all enrolled subjects)

7.6.2 Serious Adverse Events

- Summary of SAEs by CTC Grade Combined (any grade, 3-4, 5 by SOC/PT)
- Summary of SAEs by Worst CTC Grade (1, 2, 3, 4, 5 by SOC/PT)
- Summary of drug-related SAEs by Worst CTC Grade (1, 2, 3, 4, 5 by SOC/PT)
- Listing of SAEs (all enrolled subjects)

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

- Summary of AEs leading to discontinuation by CTC Grade Combined (any grade, 3-4, 5 by SOC/PT)
- Summary of AEs leading to discontinuation by Worst CTC Grade (1, 2, 3, 4, 5 by SOC/PT)
- Listing of AEs leading to discontinuation

7.6.4 All Adverse Events

- Summary of AEs by CTC Grade Combined (any grade, 3-4, 5 by SOC/PT)
- Summary of AEs by Worst CTC Grade (1, 2, 3, 4, 5 by SOC/PT)
- Summary of drug-related AEs by CTC Grade Combined (any grade, 3-4, 5 by SOC/PT)
- Summary of drug-related AEs by Worst CTC Grade (1, 2, 3, 4, 5 by SOC/PT)
- Listing of AEs

7.6.5 Multiple Adverse Events

For multiple adverse events, the following will be summarized:

- Total number and exposure-adjusted AEs summary
- Frequency of unique adverse events summary

7.6.6 Clinical Laboratory Evaluations

Laboratory results will be categorized according to NCI CTCAE grade. Analyses will be based on the international system (SI) of units, but will be repeated using US units.

Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results will compare baseline with the worst post-baseline result (up to 30 days [inclusive] after the last dose of study medication for subjects who are off-treatment).

7.6.6.1 Hematology, Serum Chemistry, and Electrolytes

- Hematology Laboratory Test Results Summary of Changes from Baseline - (hemoglobin, WBC, neutrophils [absolute], platelet count)
- Serum Chemistry Laboratory Test Results Summary of Changes from Baseline - (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, Alkaline phosphatase, Lactate dehydrogenase, Creatinine)
- Electrolytes Laboratory Test Results Summary of Changes from Baseline (sodium, potassium, chloride, calcium, phosphorus)
- Platelet count plot (% change from baseline)
- Listing of Laboratory Results Outside of Normal Range

7.6.7 Electrocardiograms

A two-sided 90% confidence interval will be constructed for the population mean of ΔQTcF at each time point. (Change from baseline in QTcF is assumed to follow a normal distribution.) The frequency distribution of QTcF and ΔQTcF will be calculated for each sampling point on Cycle 1 Day 1 and Cycle 2 Day 15. The categories for the frequency distribution will be (≤ 450 msec, 451- 480 msec, 481- 500 msec, > 500 msec) for QTcF and (≤ 30 msec, 31- 60 msec, > 60 msec) for ΔQTcF.

The following outputs will be provided:

- Summary of ECG parameters and changes from baseline by study day (descriptive statistics [n, mean, standard deviation, min, max] for HR, QT, QTcB, QTcF, PR and QRS; 90% CI for ΔQTcF)
- Frequency distribution summary of QTcF, PR, QRS and ΔQTcF (QTcF [msec: ≤ 450, 451 - 480, 481 - 500, > 500; PR [msec] : ≤ 200, > 200; QRS [msec] : ≤ 120, > 120; ΔQTcF [msec] : ≤ 30, 31 - 60, > 60)
- Listing of ECG measures (QTcF, QT, QTcB, PR, QRS, ΔQTcF, drug concentrations; flagging abnormalities)
- Plot of regression of ΔQTcF on drug concentration
- Plots of mean, and mean changes from baseline, versus time or ulocuplumab concentration may be provided

7.6.8 Vital Signs

Heart rate, body temperature, systolic and diastolic blood pressure (BP) will be analyzed. The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline (CFB) are calculated as parameter value - baseline value:

- Heart rate (bpm): value > 100 and CFB > 30, or value < 55 and CFB < -15
- Systolic BP (mmHg): value > 140 and CFB > 20, or value < 90 and CFB < -20
- Diastolic BP (mmHg): value > 90 and CFB > 10, or value < 55 and CFB < -10
- Temperature (°C): value > 38.3°C or CFB > 1.6°C

The following outputs will be provided:

- Summary of vital signs (descriptive statistics for vital signs and changes from baseline by time point)
- Listing of vital sign measures (flagging out of range measurements)

7.7 Pharmacokinetics

The PK subjects population will be used for all analyses. PK parameters will be summarized as follows:

- Cmax, Ctrough, AUC(INF), AUC(0-T), AUC(TAU), CLT, Vss: geometric means and coefficients of variation
- Tmax: median, minimum, maximum
- T-HALF: means and standard deviations

The following outputs will be provided.

- Summary of serum concentrations (summary statistics by nominal collection time)
- Summary of PK parameters (summary statistics by treatment and study day)
- Plot of individual serum concentration profiles over time
- Plot of mean (+SD) serum concentration profiles over time
- Plot of geometric mean Ctrough versus study day
- Listing of serum concentration-time profiles by actual collection time
- Listing of PK parameters (with any exclusions and reasons for exclusion)
- Listing of Ctrough values for ulocuplumab

[redacted]

[redacted].

7.9 Immunogenicity

- Immunogenicity assessments listing (with status relative to baseline: ADA negative, ADA positive, positive baseline)
- Immunogenicity assessments listing for ADA-positive subjects (with corresponding Ctrough values)

8 CONVENTIONS

Safety data will be handled according to the BMS safety data conventions (described in 'Analysis of Safety Data - Reference to CT SOP 109'). Further information regarding conventions is given in the DPP.

9 CONTENT OF REPORTS

Refer to the DPP for details of the outputs that will be produced.

10 REFERENCE

11 APPENDIX: STATISTICAL ANALYSIS PLAN FOR PHASE 1 COHORT

STUDY SPECIFIC STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

A PHASE 1, OPEN-LABEL STUDY OF ULOCUPLUMAB (BMS-936564) IN COMBINATION WITH LOW DOSE CYTARABINE IN SUBJECTS WITH ACUTE MYELOID LEUKEMIA

PROTOCOL(S) CA212016

VERSION # 1.0

TABLE OF CONTENTS

[redacted]

2 STUDY DESCRIPTION

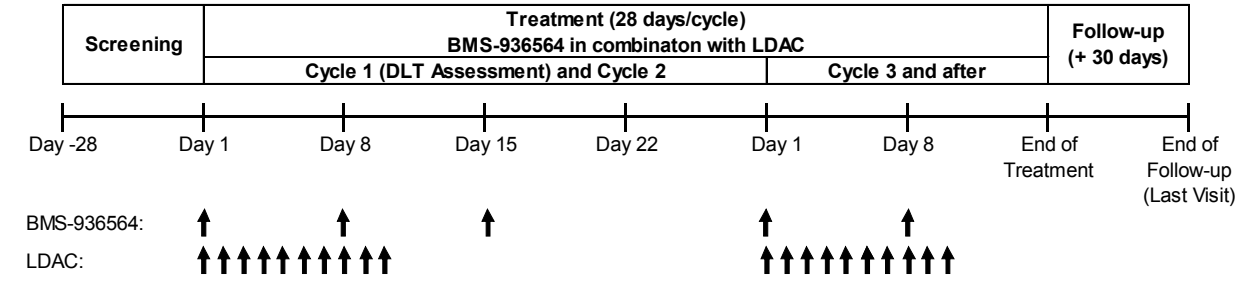
2.1 Study Design

This is a Phase 1, open-label study to assess the safety and tolerability of ulocuplumab in elderly subjects (≥ 65 years old) with newly diagnosed AML. The study will consist of 3 periods: Screening (up to 28 days), Treatment (28 days/cycle) and Follow-up (at least 30 days following the end of treatment visit). During the Treatment Period, ulocuplumab (600 mg and 800 mg) will be administered as a single intravenous (IV) infusion on Day 1, 8 and 15 in combination with low dose cytarabine (LDAC) at a total daily dose of 40 mg subcutaneously (SC) administered twice daily (20 mg BID) on Day 1 - 10 for the initial 2 cycles (28 days/cycle). This will be followed by ulocuplumab administered on Day 1 and 8 in combination with LDAC on Day 1 - 10 for subsequent cycles.

Initially 3 subjects will be treated at the dose level of 600 mg. In general, a decision to consider the next higher dose level or the next lower dose level or to stop the enrollment upon judging the current dose to be safe will be guided by the number of subjects with the dose-limiting toxicities (DLTs) observed during the DLT evaluation period based on the modified Toxicity Probability Interval (mTPI) design (see Protocol Section 3.1.1). Enrollment of the 3 subjects in the 800 mg dose level cannot begin until the third subject has completed Cycle 1 of the 600 mg dose level. DLTs are defined in Protocol Section 5.4.1. An additional dose level may also be evaluated if agreed upon by the investigators and the BMS Medical Monitor. DLTs and all other toxicities will be defined and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03). DLTs will be defined based upon events that are considered to be related to ulocuplumab in combination with LDAC and that occur during the first cycle of drug administration (28 days). A total number of 6 subjects will be treated in this study (assuming 600 mg and 800 mg are explored).

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



2.2 Treatment Assignment

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned. All enrolled subjects who meet eligibility criteria will be treated with ulocuplumab.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.

Table 1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol 01	24-Ocrt-2014	Incorporates Amendment(s) 01
Amendment 01	24-Oct-2014	This amendment of the protocol is in response to the 30-day review by Pharmaceuticals and Medical Devices Association (PMDA) for Clinical Trial Notification. Additional changes for a clarification purpose are also incorporated in this amendment.
Original Protocol	02-Sep-2014	Not applicable

3 OBJECTIVES

3.1 Primary

To assess the safety and tolerability of ulocuplumab in combination with LDAC in subjects with AML.

3.2 Secondary

- To evaluate the preliminary efficacy on the basis of objective response in subjects treated with ulocuplumab in combination with LDAC.
- To characterize the immunogenicity of ulocuplumab.

- To characterize the PK profiles of ulocuplumab in combination with LDAC.

4 ENDPOINTS

4.1 Primary Endpoint(s)

The assessment of safety will be based on DLTs occurring in Cycle 1 and adverse events (AEs), ≥ Grade 3 AEs, AEs leading to discontinuation, serious adverse events (SAEs), deaths and laboratory abnormalities in combination therapy during the Treatment period plus 30 days of follow-up. AEs and laboratory values will be graded according to NCI CTCAE v4.03.

4.2 Secondary Endpoint(s)

4.2.1 Investigator Assessed Best Overall Response (BOR)

The investigators assessed response according to the 2003 IWG-AML criteria (see Protocol Appendix 1): Complete Remission (CR), Complete Remission with incomplete blood count recovery (CRi), Partial Remission (PR), Treatment Failure (TF), Relapse (R) or Progressive Disease (PD). Leukemia responses will be recorded after each cycle as follows: CR, CRi, PR, PD, or Relapse as described above. Only if the subject never achieves a CR, CRi, or PR during the treatment period, it will be assessed as TF only for best overall response. All other subjects without these responses will be recorded as Not Applicable (NA).

4.2.2 Anti-drug Antibodies (ADA) Positive for BMS-936564

Immunogenicity of BMS-935564 is measured by the detection of human antibodies against BMS-936564. Endpoints for the study are incidence rates of persistent positive Anti-drug Antibody (ADA) as well as neutralizing positive ADA after initiation of BMS-936564.

Based on recommendation from BMS Immunogenicity Council, White Paper on Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations by Shankar et al[1], and the FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products[2], the following definitions will be applied:

Sample ADA Status**:**

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least *4*-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline

4.2.3 Pharmacokinetics Parameters for Ulocuplumab

The following PK parameters of BMS-936564 derived from serum concentration time profile of subjects will be included for PK analysis: Cmax, Ctrough, Tmax, AUC(0-T), AUC(TAU), AUC(INF), T-HALF, CLT and Vss.

5 SAMPLE SIZE AND POWER

This is a Phase 1 safety study and the sample size cannot be precisely determined and depends on the observed toxicities. It is estimated that a total of 6 subjects will be treated, assuming 600 mg and 800 mg are explored.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of three periods: pre-treatment, on-treatment, and post-treatment period for analyses.

- The pre-treatment period covers from the time of signing of the informed consent form to prior to the first dose of study medication.
- The on-treatment period starts at the time of the first dose of study medication and ends when the decision to discontinue a subject from study therapy is made.
- The post-treatment period begins when the decision to discontinue a subject from study therapy is made (no further treatment with the investigational product)

6.2 Treatment Regimens

The analysis and reporting of safety data will be performed on an as treated basis at the time of study therapy initiation unless otherwise specified.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form.
- All Treated Subjects: All subjects who received at least one dose of study medication.
- PK Subjects: All subjects who received at least one dose of BMS-936564 and have evaluable serum concentration data. Additionally, the evaluable PK subjects are defined as subjects who have evaluable PK profiles.
- Immunogenicity Subjects: All treated subjects with BMS-936564 who have baseline and at least one post baseline immunogenicity assessment.

7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher. Some figures will be generated using S-Plus.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, ie, mean, standard deviation, median, minimum and maximum values. Geometric mean and coefficient of variation will also be presented for sample serum concentration-time data and PK parameters. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100.

7.2 Study Conduct

7.2.1 Study Information

Listing:

- Batch number will be listed

7.2.2 Protocol Deviations

Relevant protocol deviations are not assessed in this study. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) protocol deviations will be reported through ClinSIGHT listings. The following programmable deviations from inclusion and exclusion criteria will be listed.

Listing:

- The deviations from inclusion and exclusion criteria collected on the CRF will be listed

7.3 Study Population

7.3.1 Subject Disposition

Summary:

- Pre-treatment period: The number (%) of subjects for the following will be summarized on the All Enrolled Subjects.
  - All enrolled into the study
  - Entering the treatment period
  - Enrolled but not entering the treatment period together with the reasons
- End of treatment period and of study: The number (%) of subjects for the following will be summarized by treatment and overall, based on the All Treated Subjects.
  - All treated subjects
  - Subjects continuing in the treatment period
  - Subjects not continuing in the treatment period together with the reasons
  - Subjects continuing in the study
  - Subjects not continuing in the study together with the reasons

Listing:

The following will be listed by subject.

- Pre-treatment period (All Enrolled Subjects): Subjects who discontinued from the study pre-treatment for screen failures
- End of treatment period (All Treated Subjects): Subjects who discontinued from the study treatment by treatment with the specific reason for discontinuation
- End of follow-up period (All Treated Subjects): Subjects who discontinued from the study with the reason for not being followed

7.3.2 Demographics and Other Baseline characteristics

Summary:

Descriptive statistics will be summarized for the following subject demographics and baseline characteristics by treatment and overall.

- Age (in years); age category (<65, ≥65 and <75, ≥75)
- Gender
- Race

Listing:

The following will be listed by subject.

- All relevant data and generally variables listed above
- Baseline disease diagnosis

7.3.3 Prior Therapy

Summary:

Descriptive statistics will be summarized for the following subject demographics and baseline characteristics by treatment and overall.

- Prior radiotherapy (Yes/No)
- Prior systemic therapy (Yes/No, the number of regimens)

Listing:

- Prior cancer therapy will be listed by subject

7.3.4 Physical measurements

Summary:

Descriptive statistics will be summarized for the following at each visit for All Treated Subjects by treatment and overall.

- Physical measurements (height, body weight, BMI and performance status (ECOG))

Listing:

- Physical measurements (height, body weight, BMI and performance status (ECOG)) will be listed by subject

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the All Treated Subjects "as treated".

7.4.1 Study Therapy

Summary:

Descriptive statistics will be provided by treatment for the following.

- Duration of therapy (days) = last dose date - first dose date + 1
  - Categories (days): 1-28, 29-56, 57-84, 85-168, >=169
- Cumulative dose (mg) = the sum of all actual doses that a subject received
- Relative dose intensity (%) = dose intensity / planned dose intensity x 100
  (* dose intensity = cumulative dose / duration of therapy)
  - <60%; 60-< 80%; 80-<90%; 90-<100%; >=100%

Listing:

The following will be listed by subject.

- All relevant data on drug administration
- Duration of therapy, cumulative dose, and relative dose intensity

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by treatment.

- Number (%) of subjects with dose interruption, dose delay, omission, and discontinuation along with the reason for study therapy modification

Listing:

- All relevant data on dose modification will be listed by subject.

7.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant medications are defined as medications other than study medications which are taken at any time on-treatment.

Summary:

The number (%) of treated subjects for the following will be provided by treatment and overall, medication class, and generic term.

- Non-study medications (prior and concomitant)

Listing:

- All prior and concomitant medications will be listed by subject.

7.5 Efficacy

Efficacy analyses will be performed on the All Treated Subjects.

Listing:

The following will be listed by subject.

- Investigator assessed subject response by visits
- Investigator assessed best overall response
- Bone Marrow Blast Assessment - bone marrow blast (%), bone marrow blast %change from baseline, and Auer Rods Presented at each visit
- Extramedullary disease - disease presence and disease site
- RBC transfusion- type of transfusion

7.6 Safety

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

AEs will be coded according to the most current version of MedDRA and be graded using the NCI CTCAE version 4.03. 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 AEs will include events occurring from the first dose date to 30 days (inclusive) after the last dose of study medication for subjects who are off study treatment.

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 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 30 days (inclusive) after the last dose of study medication 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

Summary:

AEs and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC for each treatment and overall, unless specified otherwise.

- Overall summary of any AEs presented by SOC/PT

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of any non-serious AEs presented by SOC/PT

Listing:

- All recorded AEs will be listed.

7.6.2 Deaths

Summary:

- All deaths during the study within 30 days after the last dose of study medication will be summarized for cause of deaths by treatment.

Listing:

- All recorded deaths will be listed for All Enrolled Subjects.

7.6.3 Other Serious Adverse Events

Summary:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

Listing:

- All SAEs will be listed for All Enrolled Subjects.

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

AEs 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:

- All AEs leading to discontinuation will be listed.

7.6.5 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 and overall, if appropriate, using the worst CTC grade on-treatment per subject.

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

Listing:

- The laboratory parameters will be listed by test and subject
- Laboratory abnormality criteria and laboratory results outside of normal range will be listed

7.6.6 ECGs

All available non-missing values of ECG parameters should be used in the listings, summarizations, and analyses. However,

- if QTcF is missing and RR in seconds is available, then QTcF will be calculated as
  $QTcF = QT / RR^{(1/3);}$
- if both QTcF and RR in seconds are missing, then QTcF will be calculated as
  $QTcF = QT / (60 / HR)^{(1/3).}$

Summary:

- Descriptive statistics of ECG parameters (HR, QTcF, PR and QRS) and their changes from baseline by treatment and study day
- The frequency distribution of subjects' maximum recorded post-dose QTcF, PR, QRS and ΔQTcF will be tabulated by treatment for the following ranges:
  - QTcF (msec) : ≤ 450, > 450 - 480, <480 - 500, > 500
  - PR (msec) : ≤ 200, > 200
  - QRS (msec) : ≤ 120, > 120
  - ΔQTcF (msec) : ≤ 30, > 30 - 60, > 60

Listing:

- ECG measures and abnormalities will be listed by subject
- Individual QTcF, PR, QRS or ΔQTcF values meeting these criteria will be flagged in the data listing
- Individual ΔQTcF and drug concentrations

Figure:

- Individual ΔQTcF versus drug concentrations
- Regression of ΔQTcF on drug concentrations

7.6.7 Vital Signs

Summary:

The following parameters and their corresponding change from baseline will be summarized by timepoints and treatment.

- Descriptive statistics of vital signs (systolic blood pressure, diastolic blood pressure, heart rate and body temperature) and their changes from baseline by treatment and study day

Listing:

The following will be listed by subject.

- Vital sign measures
- Vital sign measures for subject with out of range measurements

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline (CFB) are calculated as parameter value - baseline parameter value:

- Heart Rate (bpm) : Value > 100 and CFB > 30, or Value < 55 and CFB < -15
- Systolic BP (mmHg) : Value > 140 and CFB > 20, or Value < 90 and CFB < -20
- Diastolic BP (mmHg) : Value > 90 and CFB > 10, or Value < 55 and CFB < -10
- Temperature (°C) : Value > 38.3°C or CFB > 1.6°C

7.6.8 Other Safety Evaluation

Listing:

The following will be listed by subject.

- Medical History
- Physical examination
- Medical treatment procedures
- Diagnostic procedures

7.7 Immunogenicity

Listing:

- All collected immunogenicity assessment will be listed by subject.
- Immunogenicity assessment and corresponding Ctrough values for the subjects with ADA positive sample will be listed

7.8 Pharmacokinetics

The PK subjects will be used for all listings. Evaluable PK subjects will be used for summaries and statistical analyses. Analysis will include all analyte data in the PK dataset for BMS-936564.

Summary:

- Summary statistics for serum concentrations by nominal collection time and treatment
- Summary statistics for the PK parameters listed in Section 4.2.3 by treatment, study day and time
  - Geometric means and coefficients of variation for Cmax and AUC(INF), AUC(0-T), AUC(TAU), CLT and Vss
  - Median, minimum, and maximum for Tmax
  - Means and standard deviations for the PK parameters for T-HALF
  - Geometric means and coefficients of variations for Ctrough values

Figure:

- Individual plot of serum concentration profiles over time
- Mean (+SD) plot of serum concentration profiles over time
- Geometric mean of Ctrough versus study day

Listing:

The following will be listed.

- Subject serum concentration-time profiles by actual collection time
- Individual PK parameters including any exclusions and reasons for exclusion
- Exclusion flags and reasons for exclusion

8 CONVENTIONS

8.1 Safety Data Conventions

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to CT SOP 109"). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

8.2 Baseline Measurements

For laboratory measures the following will be used, in a hierarchical sequence, to select the baseline (if a criterion does not apply it would be skipped in the sequence):

- The baseline value corresponds to the last lab drawn on or prior to first dose of study drug;

- If both local and central laboratory values qualify as baseline according to the above criterion, the central laboratory value will be used as the baseline value.

For all other measures the baseline value is the last value prior to the first dose of study drug, as otherwise specified.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

10 DOCUMENT HISTORY