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CLINICAL PROTOCOL CA212016

A Phase 1/2, Open-label Randomized Study of Ulocuplumab (BMS-936564) In Combination with Low Dose Cytarabine in Subjects with Newly Diagnosed Acute Myeloid Leukemia

Revised Protocol Number: 06

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	27-Jul-2017	• The exclusion criteria was revised to specify allogeneic transplants in patients who received prior hematopoietic stem cell transplantation • The schedule for the collection of hematology samples during treatment cycles 1 and 2 was revised to eliminate the requirement for 10 days consecutive days of hematology collections, and to allow hematology sample collection flexibility up to 72 hours before infusion of ulocuplumab • Peripheral blood and serum/plasma collection criteria during End of study treatment and follow-up assessment were revised from mandatory status to include exceptions listed in Section 5.7.2 and Table 5.7.2 1 • Buccal swab procedure was added to treatment procedural outline and biomarkers sampling schedule for the expansion cohort • Time and assessment ranges were revised to reflect current standards in Sections 4.6.1.1 and 4.6.1.2 and Table 4.6.1.2-1 • Removed bone marrow collection for TCR sequencing.
Revised Protocol 05	29-Mar-2017	Incorporates Amendment 06
Amendment 06	29-Mar-2017	This amendment implements the following changes: revises synopsis to align with revisions in sections 3.1, 8.3.1 and 8.3.2; revises study design description; revises study treatment and dose timing sections to clarify when LDAC only arm may add ulocuplumab; revises discontinuation, dose modifications, infusion delays, and missed doses sections; adds whole exome sequencing to bone marrow and peripheral blood biomarker testing; revises Tables 5.1-2, 5.1-3, 5.7.2-1; moves cytogenetic testing to other assessments section; adds ECG analyses section; adds whole exome sequencing to biomarker analyses section; revises primary endpoint analysis details; revises secondary endpoint details; moves ECG analyses details from biomarker analyses section to a new section; adds cytogenetic analyses section.
Revised Protocol 04	10-Feb-2017	Incorporates Amendment(s) 05
Amendment 05	10-Feb-2017	This amendment implements the following changes: revises the telephone/fax numbers and location of the BMS Medical Monitor; corrects study title in synopsis; clarifies that exclusion criterion 2b is applicable; clarifies dose modifications and addition of ulocuplumab to LDAC alone arm; clarifies local lab bone marrow results sent to BMS; clarifies standard of care testing for extramedullary disease; adds central lab cytogenetic testing; deletes local cytogenetic testing; clarifies time point for end of cycle leukemia assessment; clarifies bone marrow aspirate is sufficient for leukemia evaluation; reduces pregnancy test requirement (WOBCP) to once per cycle and monthly during dose delays; adds pregnancy test to EOT; clarifies and/or corrects Time and Events Schedule footnotes; clarifies hematology blast percentage is included in hematology lab tests; clarifies PK, ADA, and receptor occupancy samples are not collected for subjects randomized to the LDAC alone arm; clarifies footnotes in PK and biomarker tables; clarifies safety and serial ECG requirements; provides details of

Document	Date of Issue	Summary of Change
		biomarker testing; Appendices 1 and 3 updated.
Revised Protocol 03	02-Nov-2016	Incorporates Amendment(s) 03
Amendment 03	02-Nov-2016	This amendment expands the study globally to provide insights of safety and efficacy of two different dose levels of ulocuplumab (800 mg and 1000 mg) in combination with low dose cytarabine (LDAC) and LDAC alone for the treatment of Acute Myeloid Leukemia (AML). The expansion will enroll subjects (≥ 18 years old) with newly diagnosed AML that are unfit for high induction chemotherapy or stem cell transplant because of age or comorbidities. The changes include addition of a Phase 2 (expansion cohort) with 1:1:1 randomization of approximately 120 subjects, 40 subjects per treatment group, to assess preliminary efficacy by complete remission with blast count reduction < 5% (CR) or complete remission with incomplete blood count recovery (CRi) and overall survival (OS). The changes include collection of samples for exploratory biomarker assessment such as CXR4, receptor occupancy and evaluation of ulocuplumab pharmacokinetics and interaction with LDAC. For safety, DLTs will be evaluated and ECG evaluation was added for a subset of subjects to measure QT intervals by Fridericia method.
Revised Protocol 02	07-May-2015	Incorporates Administrative Letter 01 and Amendment(s) 02
Amendment 02	07-May-2015	This amendment of the protocol is to implement following changes: modify the target population to remove the restriction on AML (newly diagnosed, elderly), extend the period of contraception use, modify prior therapy related criteria, and modify hepatitis B and C infection criteria to only exclude active infection.
Administrative Letter 01	05-Jan-2015	To change Medical Monitor
Revised Protocol 01	24-Oct-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

OVERALL RATIONALE FOR THE REVISED PROTOCOL 06

The rationale for Revised Protocol 06 is to allow flexibility with regard to the hematology testing window and to add buccal swab collection as germline control for whole exome sequencing analysis. In addition, clarification of exclusion criteria for prior hematopoietic stem cell transplantation, peripheral blood collection during end of treatment (EOT) and Follow-up period were made.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06

Section Number & Title	Description of Change	Brief Rationale
Section 3.3.2 Exclusion Criteria, item 2 e	This exclusion criterion was revised to specify allogeneic transplants in patients who received prior hematopoietic stem cell transplantation	[redacted]
Section 4.6.1.1 Treatment Discontinuation Criteria; Section 4.6.1.2 Dose Modifications, Infusion Delays and Missed Doses; Table 4.6.1.2-1 Dose Delay and Discontinuation Criteria for Ulocuplumab-related Adverse Events.	Time and assessment ranges were revised as follows: • Discontinuation due to prolonged bone marrow suppression was revised from > 56 days to ≥ 56 days • For dose delay, the definitions of myelosuppression as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with < 5% blasts were revised from < to ≤ in all instances • Discontinuation due to QT prolongation was revised from QTcF > 500 msec ≥ 500 msec. • For dose delay and discontinuation, definition of Grade 3 baseline neutrophil count was revised from < 1000 cells/μL to ≤ 1000 cells/μL • Definition of continuous study treatment delay was revised from > 56 days to ≥ 56 days.	
Section 5.1 Flow Chart/Time and Events Schedule; Table 5.1-2 Treatment Procedural Outline (CA212016), Hematology	The schedule for the collection of hematology samples during treatment cycles 1 and 2 was revised to eliminate the requirement for 10 consecutive days of hematology collections.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 Flow Chart/Time and Events Schedule; Table 5.1-2 Treatment Procedural Outline (CA212016), Peripheral blood and serum/plasma; Table 5.1-3: Follow-up Assessments (CA212016), Peripheral blood and serum/plasma	Peripheral blood and serum/plasma collection criteria during study treatment and follow-up assessment were revised from mandatory status to include exceptions listed in Section 5.7.2 and Table 5.7.2-1.	[redacted]
[redacted]	[redacted]	[redacted]
Section 5.7.1 Bone Marrow Testing Section 8.4.7 Biomarker Analyses	Revised to remove bone marrow collection for TCR sequencing	[redacted]
All	Minor formatting and typographical corrections	[redacted]

SYNOPSIS

Clinical Protocol CA212016

Protocol Title: 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

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Ulocuplumab (600 mg-escalation cohort and 800 mg-escalation and expansion cohorts, 1000 mg expansion cohort) will be administered as a single intravenous (IV) infusion over approximately 60 minutes on Day 1, 8, and 15 in combination with low dose cytarabine (LDAC) (20 mg BID [(40 mg/day], SC) administered on Day 1-10 for each cycle (28 days/cycle) of the initial 2 cycles (Cycle 1-2). For Cycle 3 and subsequent cycles (28 days/cycle), subjects will receive ulocuplumab (600, 800 or 1000 mg, IV) on Day 1 and 8 in combination with LDAC (20 mg BID, SC) on Day 1 - 10. Subjects who are tolerating study treatment, clinically stable and not progressing rapidly at the end of each cycle may continue additional cycles until disease progression, development of unacceptable toxicity, intercurrent illness preventing treatment, or patient/physician request. For subjects randomized to the LDAC only arm, they will receive LDAC (20 mg BID, SC) on Day 1-10.

Study Phase: 1/2

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

Rationale: The first 6 AML subjects (3 de novo, 1 AML relapsed, 2 secondary AML to myelodysplasia and myelofibrosis) in the escalation cohort of this trial (CA212016) were treated at dose levels of 600 mg and 800 mg ulocuplumab in combination with LDAC 20 mg BID. Overall complete remission/complete remission with incomplete blood count (CR/CRi), as assessed by the investigator, was observed in 4 of 6 evaluable subjects (66%), with 1 of 4 responders treated at 60 0mg and 3 of 4 responders at 800 mg. Based on the results from the escalation cohort, a Phase 2 (expansion cohort) was added to this protocol

In the Phase 2 (expansion cohort), a randomization ratio of 1:1:1 was selected to include two doses of ulocuplumab (800 mg and 1000 mg) in combination with LDAC and LDAC alone. In each arm a sample size of approximately 40 subjects per treatment group will allow estimation of the complete response rate.

Primary Objective:

In Phase 1 (escalation cohort): To assess the safety and tolerability of ulocuplumab in combination with low-dose cytarabine (LDAC) in subjects with AML.

In Phase 2 (expansion cohort): 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 low-dose cytarabine (LDAC).

Secondary Objectives:

- 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
- In Phase 1 (escalation cohort): To evaluate the preliminary efficacy on the basis of objective response in subjects treated with ulocuplumab in combination with LDAC.
- To assess overall survival (OS) in subjects treated with ulocuplumab 800 mg or 1000 mg in combination with LDAC.
- In Phase 2 (expansion cohort): 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.
- In Phase 2 (expansion cohort): To assess rates of overall remission (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.

- In Phase 2 (expansion cohort): To assess efficacy (in terms of rates of CR/CRi and OR and duration of remission, 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.

[redacted]

Study Design: In the escalation phase, this was a Phase 1, open-label study to assess the safety and tolerability of ulocuplumab in subjects with AML. The study consisted 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). Escalation phase subjects will be followed for overall survival (OS) for at least 2 years. The dose of ulocuplumab chosen to be explored in the escalation cohort of this study (600 mg and 800 mg) was selected based on the results from a Phase 1 study (CA212001).

Based upon the CA212016 escalation cohort results, the protocol is revised to include an exploratory, non-comparative open-label Phase 2 expansion cohort of up to approximately an additional 120 AML subjects. Expansion cohort subjects will be randomized to 1 of 3 treatment arms: LDAC alone or either 800 mg or 1000 mg ulocuplumab in combination with LDAC 20 mg BID. Escalation cohort subjects who are continuing treatment will continue at their assigned dose. In the expansion cohort, randomization will be suspended in the ulocuplumab 1000 mg arm while safety data from the first 6 subjects in this arm are evaluated for DLTs. For the escalation and expansion cohorts, DLTs and all other toxicities were defined and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03). DLTs were defined based upon events that were considered to be related to ulocuplumab in combination with LDAC and that occurred during the first cycle of drug administration (28 days).

The Screening Period is defined as 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.

During the Treatment Period of the escalation and expansion arms, ulocuplumab (600, 800 or 1000 mg, IV) will be administered on Day 1, 8 and 15 in combination with LDAC (20 mg BID (40 mg/day), SC) administered on Day 1-10 for each cycle (28 days/cycle) of the initial 2 cycles (Cycle 1-2). For Cycle 3 and subsequent cycles (28 days/cycle), subjects will receive ulocuplumab (600, 800 or 1000 mg, IV) on Day 1 and 8 in combination with LDAC (20 mg BID, SC) on Day 1 - 10. Subjects who are tolerating study treatment, clinically stable and not progressing rapidly at the end of each cycle may continue 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. For subjects randomized to the LDAC alone arm, they will receive LDAC (20 mg BID, SC) on Day 1-10.

Leukemia response assessment will be evaluated for each cycle using the 2003 International Working Group Response Criteria for AML (AML IWG 2003). The results of the response assessments must be reviewed and documented before the first dose of the next cycle.

Subjects who experience study drug-related AEs that are ongoing at the follow-up visit will continue to be followed until the AEs are (i) resolved to baseline, (ii) stabilized, or (iii) have been deemed irreversible unless further anti-cancer treatment are administered.

Subjects who discontinue study treatment for any reasons will be followed for 30 days after the end of treatment visit for AEs. Subjects will be followed for overall survival for 2 years.

The last visit for each subject will be defined as the end of follow up visit which is no less than 30 days after the subject's end-of-treatment visit.

The study will end after the last subject completes the last visit.

A total number of up to approximately 126 (6 escalation cohort and 120 expansion cohort) subjects will be treated in this study. The entire study (Screening, Treatment and Follow-up) is expected to last approximately 7 years, with the addition of the expansion cohort and overall survival follow up.

The expansion phase of the study will include approximately 120 subjects in order to randomize subjects in a 1:1:1 ratio: 40 subjects in the ulocuplumab 800mg plus LDAC arm, 40 subjects in the ulocuplumab 1000 mg plus LDAC arm and 40 subjects in the LDAC alone arm (Figure 2). The randomization will be suspended in the ulocuplumab 1000 mg arm while the safety data on the first 6 subjects on this arm are evaluated for DLTs. Randomization will continue in the other 2 arms while the data is reviewed therefore total numbers randomized is approximate. Randomization to the 1000 mg ulocuplumab 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.

Subjects in the LDAC alone arm will be permitted to add ulocuplumab 800 mg into their treatment regimen if they do not achieve complete remission (CR or complete remission with incomplete blood count recovery [CRi]) confirmed by blast count reduction after 4 treatment cycles or if they relapse after achieving complete remission. If ulocuplumab is added to the LDAC alone arm, the treatment schedule is LDAC 20 mg BID from day 1 to 10 of each cycle and ulocuplumab 800mg on Day 1, 8 and 15 for the first 2 cycles then ulocuplumab 800 mg on Day 1 and 8 for subsequent cycles.

The study design schematic is presented in Figure 1.

Figure 1: **Study Design Schematic**

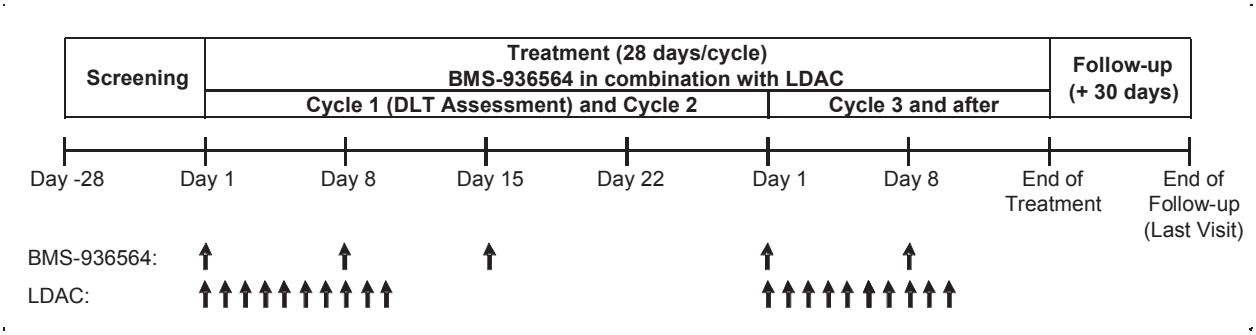
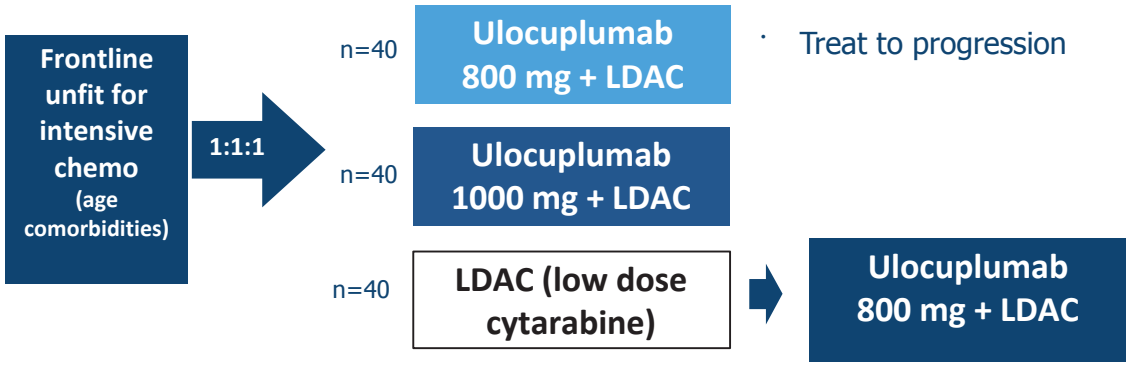


Figure 2: **Phase 2 Study Design Schematic**



Physical examinations/measurements, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times. Subjects will be closely monitored for AEs throughout the study. Blood samples will be collected for PK, RO and immunogenicity analyses. Blood and bone marrow aspirate samples will be collected for biomarker analyses. A minimum of 15 subjects each from the 800 mg and 1000 mg expansion cohorts are required to provide serial blood samples and time-matched ECGs to further characterize the PK of ulocuplumab and its effect on ECG intervals in combination with LDAC (Serial PK/ECG Subset).

The expansion cohort will treat approximately an additional 120 subjects at a dose of 800 mg or 1000 mg ulocuplumab in combination with LDAC or LDAC alone. All assessments from the escalation cohort will be performed and additional assessments will be completed (e.g., biomarkers, overall survival, serial ECGs).

Follow-up

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will have one follow-up visit for safety. Follow-up visit 1(X01) will be completed 30 days (± 7 days) from the last dose of study therapy. After X01, subjects will be followed every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent. Subjects will also be followed every 3 months for survival for up to two years, until death, lost to follow-up or withdrawal of study consent.
- PK, immunogenicity and biomarker samples will be collected at the 30 day follow-up visit.

Dose Escalation:

In the escalation cohort, enrollment of subjects adhered to a Modified Toxicity Probability Interval (mTPI) design. The study design set a 20% target DLT rate with an equivalence interval of 15 - 25%. Initially 3 subjects treated at the dose level of 600 mg. No additional subjects were added to the same dose level (i.e., a total number of 3 subjects were treated for a given dose level). 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 was guided by the number of subjects with DLTs observed during the DLT evaluation period based on the mTPI design (Table 1).

Table 1: Guidance for Safety Monitoring Based on Observed Toxicity Outcomes (Escalation Cohort Only)

		Number of Subjects Treated at Given Dose Level
		3
Number of Subjects with DLTs	0	E
	1	E
	2	DU
	3	DU

At Starting Dose (600 mg):

E: Escalate and enroll subjects to the next higher dose level

DU: The current dose is too toxic. Discuss of proceeding with the next lower dose level

At Maximum Dose (800 mg):

E: The current dose level is safe and stop enrollment

DU: The current dose is too toxic

No subject will be permitted intra-subject dose escalations. Subjects who withdraw from the study during Cycle 1 for reasons other than a DLT may be replaced. Subjects who have not received complete doses (all the doses of

ulocuplumab and cytarabine specified in the protocol) during Cycle 1 may also be replaced. Depending on toxicity, an additional dose level may be defined after discussion with the BMS Medical Monitor and investigators.

In the expansion cohort, there is no dose escalation provision.

Study Population: Subjects with AML.

Study Drug: Includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug CA212016		
Medication	**Potency**	**IP/Non-IP**
Ulocuplumab Injection	10 mg/mL	IP
Cytarabine	Refer to package insert	IP

Study Assessments:

Safety Outcome Measures:

The following safety assessments will be performed during the study: vital sign measurements, clinical laboratory tests, bone marrow tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, physical examinations/measurements, ECGs (12-lead), concomitant medications, transfusions, and the incidence and severity of AEs.

Efficacy Measures:

Efficacy assessments will be determined by changes in bone marrow aspirate/biopsy, hematological laboratory tests, red blood cell transfusion dependency, and assessments for extramedullary disease (if applicable). Leukemia response assessment will be evaluated using AML IWG 2003. Rate and duration of complete remission will be summarized. Overall survival (OS) will also be assessed. Primary efficacy analyses will be based on the best overall response.

PK Measures:

Serial and sparse PK samples will be collected in all subjects from the escalation and expansion cohorts.

PK parameters including Cmax, Ctrough, Tmax, AUC(0-T), AUC(TAU), AUC(INF), CLT, and Vss will be derived from serum concentration versus actual time data for ulocuplumab. AUC(INF) after first dosing and T-HALF will be calculated when possible. Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program.

Immunogenicity Assessments:

Development of anti-drug antibodies (ADA) to ulocuplumab will be evaluated.

Biomarker Assessments (Expansion Cohort only)

Exploratory biomarkers in bone marrow aspirate and peripheral blood will be evaluated, including receptor occupancy (RO).

Other Assessments

Serial ECGs will be obtained from a subset of subjects in the expansion cohort (a minimum of 15 subjects per dose level, Serial PK/ECG Subset) and will be assessed by an independent core laboratory.

Statistical Considerations

Sample Size:

The size of the study is not based on testing a formal statistical hypothesis. The Escalation Cohort is a Phase 1 safety phase 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 in this cohort, assuming 600 mg and 800 mg are explored. For the Expansion Cohort (Phase 2), 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=CR+CRi). A response rate of 0.6 will be estimated with the following 95% exact confidence interval (CI): 0.43 - 0.75. If the response rate is 0.45, then the associated 95% CI will be 0.29 - 0.62.

Endpoints:

Primary Endpoints:

- Phase 1 (escalation cohort): DLTs in Cycle 1, and AEs, ≥ Grade 3 AEs, AEs leading to discontinuation, SAEs, deaths and laboratory abnormalities in combination therapy during the Treatment period plus 30 days of follow-up will be the primary endpoints for this study. AEs will be graded according to NCI CTCAE v4.03
- Phase 2 (expansion cohort): Investigator will assess best overall response. The primary endpoint will be based on the 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). The primary analysis will be conducted after all patients had an opportunity for 6 months of follow-up.

Secondary Endpoints:

- Phase 1 (escalation cohort): Investigator assessed best overall response prior to the initiation of any alternative therapy.
- Phase 2 (expansion cohort): 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 will be the primary endpoints for this study. AEs will be graded according to NCI CTCAE v4.03.
- ADA positive for ulocuplumab.
- The PK parameters including Cmax, Ctrough, Tmax, AUC(0-T), AUC(TAU), AUC(INF), T-HALF, CLT and Vss.
- In Phase 2 (expansion cohort): To assess rates of Overall Remission (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.
- In Phase 2 (expansion cohort): To assess efficacy (in terms of rates of CR/CRi and OR and duration of remission, 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.
- Duration of remission (DoR) is defined as the time from the date of first documented CR or 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.
- 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 hear rate correction.)
- Overall survival (OS) will also be summarized. OS is defined as 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.

[redacted]

Analyses:

Safety Analysis:

All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs, clinical laboratory test results and any significant physical examination findings will be listed and summarized by treatment. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. To assess the effects of ulocuplumab on heart rate, PR, QRS, QT, QTcF, and ΔQTcF intervals, the frequency distribution for maximum QTcF, PR, QRS and the maximum ΔQTcF will be tabulated. For QTcF a linear regression of ΔQTcF on drug concentration will be estimated. Summary statistics will be tabulated for all ECG parameters and changes from baseline. The plots of mean and mean changes from baseline versus time or ulocuplumab concentration may be provided. A two-sided 90% confidence interval will be constructed for the population mean of ΔQTcF at each time point.

PK Analysis:

Summary statistics will be tabulated for the PK parameters and RO by treatment and study day. Geometric means and coefficients of variation will be presented for Cmax, AUC and CL. Medians, minimum, and maximum will be presented for Tmax. Means and standard deviations will be provided for the remaining PK parameters. Individual as well as mean concentration-time plots will be depicted.

The distribution of Ctrough concentrations will be summarized using descriptive statistics by treatment and study day. To assess the attainment of steady state, geometric mean Ctrough values will be plotted by treatment and study day.

Changes of CXCR4 RO is related to the dose and exposure of ulocuplumab. The association between the percent of RO and ulocuplumab serum concentration in peripheral blood and, when possible, bone marrow will be explored.

Efficacy Analysis:

Individual tumor responses will be listed by treatment and study day. Bone marrow blast and its percent change from baseline will be listed.

In addition, for the expansion cohort, best overall response prior to the initiation of any alternative therapy (including any subsequent ulocuplumab 800 mg for subjects in the LDAC alone arm) will be tabulated. 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. The combined rate of subjects with responses of either CR or CRi or PR will similarly be summarized.

OS and DoR will be summarized descriptively using Kaplan-Meier methodology. Median values of OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method considering a log-log transformation, will be calculated.

Immunogenicity Analysis: Listings for ADA positive response will be provided by treatment.

[redacted]

Interim Analysis:

For the dose expansion cohort, an interim assessment of safety will be assessed by Sponsor or designee on the first 6 patients treated on the 1000 mg ulocuplumab/LDAC combination arm. These must have had an opportunity for at least 28 days of follow-up. The review will be based all available safety data including DLTs reported during the first 28 days of follow-up. Randomization to the 1000 mg ulocuplumab combination arm will be suspended until the safety review is complete. Randomization to the other 2 arms will continue on a 1:1 basis until a decision is reached to resume randomization to all 3 arms.

In addition, an interim analysis of efficacy and safety will be conducted when 60 patients (i.e., 50% of the sample size) will have had an opportunity for 2 months of treatment and follow-up.

Data Monitoring Committee

An independent data monitoring committee (DMC) will be constituted for review of safety information and assessment of overall benefit/risk balance in this study. Specific data to be reviewed and timing of the reviews by the DMC will be described in a DMC Charter.

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1 INTRODUCTION AND STUDY RATIONALE

This Phase 1/2 randomized study will evaluate the safety and tolerability of ulocuplumab (BMS-936564) in subjects with acute myeloid leukemia (AML). Ulocuplumab (600 mg, 800 mg and 1000 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. In addition, the efficacy, pharmacokinetics (PK) and immunogenicity of ulocuplumab when added to LDAC will be assessed. The phase 1 dose escalation includes newly diagnosed or relapsed subjects with AML unfit for intensive chemotherapy. The phase 2 expansion cohorts will include newly diagnosed AML patients unfit for intensive chemotherapy.

[redacted]

1.2 Research Hypothesis

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

1.3 Objectives(s)

1.3.1 Primary Objectives

In Phase 1 (escalation cohort): To assess the safety and tolerability of ulocuplumab in combination with low-dose cytarabine (LDAC) in subjects with AML.

In Phase 2 (expansion cohort): 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 low-dose cytarabine (LDAC).

1.3.2 Secondary Objectives

- 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
- In Phase 1 (escalation cohort): To evaluate the preliminary efficacy on the basis of objective response in subjects treated with ulocuplumab in combination with LDAC.

- To assess overall survival (OS) in subjects treated with ulocuplumab 800 mg or 1000 mg in combination with LDAC.
- In Phase 2 (expansion cohort): 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.
- In Phase 2 (expansion cohort): To assess rates of overall remission (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.
- In Phase 2 (expansion cohort): To assess efficacy (in terms of rates of CR/CRi and OR and duration of remission, 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.

1.5 Overall Risk/Benefit Assessment

Patients with AML who are unfit for intensive chemotherapy have treatment options with low complete response rates without prolonged survival. This majority of patients with AML represents a high unmet medical need. Allogeneic stem cell transplant is not a treatment option for patients who are unfit for intensive chemotherapy. The potential benefit to subjects who are treated in this study is the possibility that clinical response will be achieved. However, experience with ulocuplumab to date is limited.

Primary safety concerns identified for ulocuplumab in pivotal 1-month repeat dose toxicology studies in monkeys were anaphylactic reactions, leukocytosis, alterations in trafficking of B- and T-lymphocytes within lymphoid tissues, and transient thrombocytopenia.

As of 26-Feb-2016, data in 73 subjects with relapsed/refractory AML from CA212001 indicate that ulocuplumab was well tolerated in these subjects as monotherapy and in combination with MEC chemotherapy. In the escalation phase and initial safety expansion, 30 relapsed AML subjects were treated at dose levels of 0.3, 1, 3, and 10 mg/kg. Overall complete remission/complete remission with incomplete blood count (CR/CRi) was observed in 18-50% of subjects at the dose levels evaluated. In the dose expansion component, 9% of subjects attained CR/CRi after a single dose of ulocuplumab. Additionally, relapsed AML subjects treated with combination ulocuplumab and MEC chemotherapy were studied in 2 cohorts: those with CR1 > 6 months (n = 23) and those with CR1 ≤ 6 months or primary induction failure (n = 20). The overall complete remission rate (CR/CRi) was 51%. The complete remission rate was 70% and 30% among subject with CR1 > 6 months and ≤ 6 months, respectively.

Preliminary efficacy data are available from the escalation cohort of this trial, CA212016. In the escalation cohort, 6 AML subjects were treated at dose levels of 600 mg and 800 mg in combination with LDAC 20 mg BID. Overall complete remission/complete remission with incomplete blood count (CR/CRi) was observed in 4 of 6 evaluable subjects (66%), with 1 of 4 responders treated at 600 mg and 3 of 4 responders at 800 mg.

Based on data from CA212016 escalation phase data and nonclinical toxicology studies of ulocuplumab, there is a possibility of hematologic toxicity. Intensive safety monitoring is included in CA212016 to allow investigators to recognize toxicities that may be related to ulocuplumab or to the potentiating of chemotherapy-associated toxicities. The protocol contained inclusion and exclusion criteria appropriate to the population, instructions for screening tests, AE monitoring and dose modification guidelines. AEs and SAEs were reviewed on an ongoing basis by the BMS Medical Monitor to look for and identify significant trends and safety issues at the earliest point.

Because there was a single Grade 3 infusion-related reaction in a DLBCL subject in CA212001, if a subject experiences a Grade 2 infusion reaction with ulocuplumab, the subject is required to receive prophylactic premedication for subsequent infusions of ulocuplumab. The pre-medications included, but not limited to, diphenhydramine, acetaminophen, and low-dose corticosteroids, which pose minimal risk to subjects in the dose and frequency given. If a subject experiences a Grade ≥ 3 infusion reaction, the subject discontinued the study treatment. Therefore, the overall risk/benefit assessment did not change.

Based on preliminary clinical experience with another CXCR4-targeted agent, non-clinical studies of ulocuplumab that indicate anti-tumor activity in AML models, and the acceptable clinical safety profile and preliminary efficacy data for AML subjects observed in CA212001 and CA212016 to date, ulocuplumab in combination with chemotherapy may be a promising therapeutic approach for further investigation and its potential benefits appear to outweigh any potential risks.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval of the written informed consent form and any other information to be provided to the subjects, via the head of the study site, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the head of the study site, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the

subject's willingness to continue participation in the study. This communication should be documented.

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

The consent form must also include a statement that BMS, the IRB/IEC, and regulatory authorities have direct access to subject records.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

In the escalation phase, this was a Phase 1, open-label study to assess the safety and tolerability of ulocuplumab in subjects with AML. The study consisted 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). Escalation phase subjects will be followed for overall survival (OS) for at least 2 years. The dose of ulocuplumab chosen to be explored in the escalation cohort of this study (600 mg and 800 mg) was selected based on the results from a Phase 1 study (CA212001).

Based upon the CA212016 escalation cohort results, the protocol is revised to include an exploratory, non-comparative open-label Phase 2 expansion cohort of up to approximately an additional 120 AML subjects. Expansion cohort subjects will be randomized to 1 of 3 treatment arms: LDAC alone or either 800 mg or 1000 mg ulocuplumab in combination with LDAC 20 mg BID (Figure 3.1-2). Escalation cohort subjects who are continuing treatment will continue at their assigned dose. In the expansion cohort, randomization will be suspended in the ulocuplumab 1000 mg arm while safety data from the first 6 subjects in this arm are evaluated for DLTs. For the escalation and expansion cohorts, DLTs and all other toxicities were defined and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03). DLTs were defined based upon events that were considered to be related to ulocuplumab in combination with LDAC and that occurred during the first cycle of drug administration (28 days).

The Screening Period is defined as 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.

During the Treatment Period of the escalation and expansion arms, ulocuplumab (600, 800 or 1000 mg, IV) will be administered on Day 1, 8 and 15 in combination with LDAC (20 mg BID (40 mg/day), SC) administered on Day 1-10 for each cycle (28 days/cycle) of the initial 2 cycles (Cycle 1-2). For Cycle 3 and subsequent cycles (28 days/cycle), subjects will receive ulocuplumab (600, 800 or 1000 mg, IV) on Day 1 and 8 in combination with LDAC (20 mg BID, SC) on Day 1 - 10. Subjects who are tolerating study treatment, clinically stable and not progressing rapidly at the end of each cycle may continue 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. For subjects randomized to the LDAC alone arm, they will receive LDAC (20 mg BID, SC) on Day 1-10.

Leukemia response assessment will be evaluated for each cycle using the AML IWG 2003 (Appendix 1). The results of the response assessments must be reviewed and documented before the first dose of the next cycle.

Subjects who experience study drug-related AEs that are ongoing at the follow-up visit will continue to be followed until the AEs are (i) resolved to baseline, (ii) stabilized, or (iii) have been deemed irreversible unless further anti-cancer treatment are administered.

Subjects who discontinue study treatment for any reasons will be followed for 30 days after the end of treatment visit for AEs. Subjects will be followed for overall survival for 2 years.[29]

The last visit for each subject will be defined as the end of follow up visit which is no less than 30 days after the subject's end-of-treatment visit.

The study will end after the last subject completes the last visit.

A total number of up to approximately 126 (6 escalation cohort and 120 expansion cohort) subjects will be treated in this study. The entire study (Screening, Treatment and Follow-up) is expected to last approximately 7 years, with the addition of the expansion cohort and overall survival follow up.

The expansion phase of the study will include approximately 120 subjects in order to randomize subjects in a 1:1:1 ratio: 40 subjects in the ulocuplumab 800 mg plus LDAC arm, 40 subjects in the ulocuplumab 1000 mg plus LDAC arm and 40 subjects in the LDAC alone arm (Figure 3.1-2). The randomization will be suspended in the ulocuplumab 1000 mg arm while the safety data on the first 6 subjects on this arm are evaluated for DLTs. Randomization will continue in the other 2 arms while the data is reviewed therefore total numbers randomized is approximate. Randomization to the 1000 mg ulocuplumab 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.

Subjects in the LDAC alone arm will be permitted to add ulocuplumab 800 mg into their treatment regimen if they do not achieve complete remission (CR or complete remission with incomplete blood count recovery [CRi]) confirmed by blast count reduction after 4 treatment cycles or if they relapse after achieving complete remission. If ulocuplumab is added to the LDAC alone arm, the treatment schedule is LDAC 20 mg BID from Day 1 to 10 of each cycle and ulocuplumab 800 mg on day 1, 8 and 15 for the first 2 cycles then ulocuplumab 800 mg on Day 1 and 8 for subsequent cycles.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic

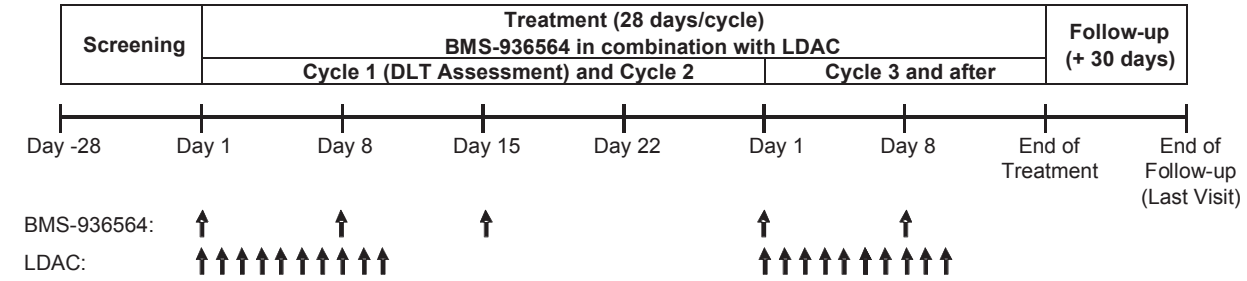
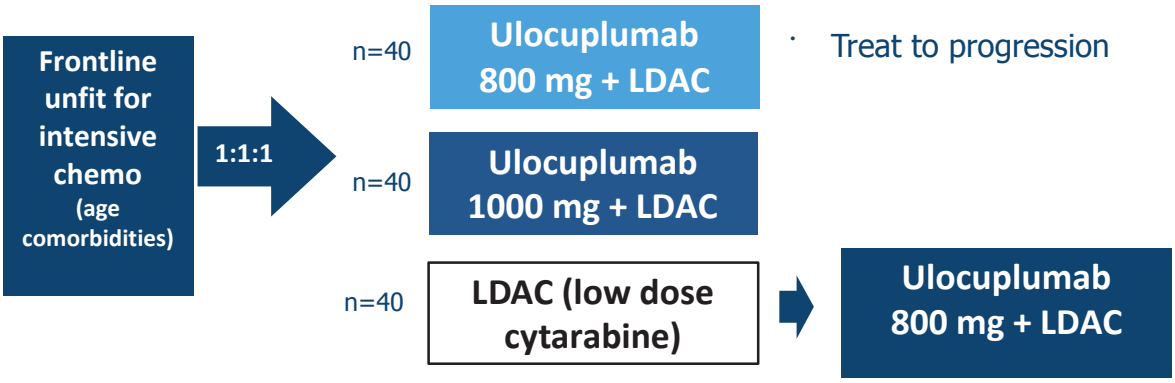


Figure 3.1-2: Phase 2 Study Design Schematic



Physical examinations/measurements, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times. Subjects will be closely monitored for AEs throughout the study. Blood samples will be collected for PK, RO and immunogenicity analyses. Blood and bone marrow aspirate samples will be collected for biomarker analyses. A minimum of 15 subjects each from the 800 mg and 1000 mg expansion cohorts are required to provide serial blood samples and time-matched ECGs to further characterize the PK of ulocuplumab and its effect on ECG intervals in combination with LDAC (Serial PK/ECG Subset, Table 5.5.1-1).

The expansion cohort will treat approximately an additional 120 subjects at a dose of 800 mg or 1000 mg ulocuplumab in combination with LDAC or LDAC alone. Sample size is discussed in Section 8.1. All assessments from the escalation cohort will be performed and additional assessments (eg, biomarkers) are noted in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.5.1-1, Table 5.5.1-2, and Table 5.7.2-1.

Follow-up

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will have one follow-up visit for safety. Follow-up visit 1(X01) will be completed 30 days (± 7 days) from the last dose of study therapy. After X01, subjects will be followed

every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent. Subjects will also be followed every 3 months for survival for up to two years, until death, lost to follow-up or withdrawal of study consent.

- PK, immunogenicity and biomarker samples will be collected at the 30 day follow-up visit.

3.1.1 Dose Escalation

In the escalation cohort, enrollment of subjects adhered to a Modified Toxicity Probability Interval (mTPI) design. The study design set a 20% target DLT rate with an equivalence interval of 15 - 25%. Initially 3 subjects were treated at the dose level of 600 mg. No additional subjects were added to the same dose level (ie, a total number of 3 subjects were treated for a given dose level). 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 was guided by the number of subjects with DLTs observed during the DLT evaluation period based on the mTPI design (see Table 3.1.1-1). The performance of the design is reported in Appendix 2.

Table 3.1.1-1: Guidance for Safety Monitoring Based on Observed Toxicity Outcomes (Escalation Cohort Only)

		Number of Subjects Treated at Given Dose Level
		3
Number of Subjects with DLTs	0	E
	1	E
	2	DU
	3	DU

At Starting Dose (600 mg):

E: Escalate and enroll subjects to the next higher dose level

DU: The current dose is too toxic. Discuss of proceeding with the next lower dose level

At Maximum Dose (800 mg):

E: The current dose level is safe and stop enrollment

DU: The current dose is too toxic

- No subject will be permitted intra-subject dose escalations.
- Subjects who experience a DLT during Cycle 1 (DLT evaluation period) will not receive further study treatment. Subjects who withdraw from the study during Cycle 1 for reasons other than a DLT may be replaced. Subjects who have not received complete doses (all the doses of ulocuplumab and cytarabine specified in the protocol) during Cycle 1 may also be replaced.
- Depending on toxicity, an additional dose level may be defined after discussion with the BMS Medical Monitor and investigators.

In the expansion cohort, there is no dose escalation provision.

3.2 Post Study Access to Study Drug

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1 of Cycle 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) The signed informed consent form. Willing and able to give informed consent; this must be obtained before performing protocol-related procedures that are not part of standard patient care.

2. Target Population

a) Subjects who were newly diagnosed with acute myeloid leukemia based on WHO classification (de novo or secondary) with minimum blast count of 20% (Appendix 3).

b) Investigator considers that subject is inappropriate for intensive remission induction therapy[30] and eligible for LDAC treatment if at least one of the following criteria are met:

i) Age older than 70 years[31,32]

ii) ECOG performance status 3

iii) Congestive heart failure or documented cardiomyopathy with an EF ≤50%

iv) Creatinine ≥ 1.3 mg/dL

v) Hematopoietic Cell Transplant-comorbidity index (HCT-CI) ≥ 3[33,34] (Appendix 6)

vi) Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

c) Not eligible for stem cell transplantation (SCT).

d) Radiation therapy to chloromas allowed but irradiated lesion may not be used to assess response.

e) Screening laboratory values must meet the following criteria:

i) WBC < 100,000/μL

ii) Creatinine ≤ 2.0 mg/dL

iii) Aspartate aminotransferase (AST) ≤ 3 × upper limit of normal (ULN)

iv) Alanine aminotransferase (ALT) ≤ 3 × ULN

v) Total bilirubin ≤ 2.0 mg/dL

f) Life expectancy at least 12 weeks.

g) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 3 (Appendix 4).

h) Not positive for human immunodeficiency virus (HIV).

i) No active hepatitis B or C infection. (Does not include positive serologies resulting from passive transfer of antibodies, eg IVIG).

j) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Adults age ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding (Even if breastfeeding is discontinued, the participation to the study is not allowed).

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s), ulocuplumab and LDAC, plus 5 half-lives of study drug (48 days) plus 30 days (duration of ovulatory cycle) for a total of 78 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s), ulocuplumab and LDAC, plus 5 half-lives of the study drug (48 days) plus 90 days (duration of sperm turnover) for a total of 138 days post-treatment completion.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (Appendix 5). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Acute promyelocytic leukemia (FAB classification M3).

b) Current Myelodysplastic Syndrome (MDS) with blast percentage < 20%

2. Previous and Concurrent Therapies

a) Prior therapy for AML, except for hydroxyurea which can be continued up to Day 21 of Cycle 1.

b) No new investigational therapies for any reason shall be initiated within 4 weeks prior to the first dose of ulocuplumab and also while the subject is participating in the study.

c) Concomitant use of other AML systemic therapy may not be used while the subject is participating in the study while receiving ulocuplumab or LDAC as part of treatment period.

d) Subjects taking oral or parenteral corticosteroids must be tapered off this medication prior to the first dose of ulocuplumab and must remain discontinued from all oral and parenteral corticosteroids while participating in the study (unless used for treatment of infusion reactions, rash or antiemetic prophylaxis or subjects on low-dose corticosteroids [< 20 mg prednisone or equivalent] for chronic conditions).

e) Prior allogeneic hematopoietic stem cell transplant

3. Medical History and Concurrent Diseases

a) AML subjects with signs or symptoms of leukostasis/hyperleukocytosis that could be exacerbated by ulocuplumab.

b) Unstable angina or uncontrolled congestive heart failure.

c) Any of the following on 12-lead electrocardiogram (ECG) prior to ulocuplumab administration, confirmed by repeat:

i) PR ≥ 220 msec

ii) QRS ≥ 120 msec

iii) QT ≥ 500 msec

iv) QTc ≥ 450 msec (Fridericia correction)[35]

d) Any other malignancy, excluding basal or squamous cell carcinoma of the skin, in situ melanoma, cervical carcinoma in situ, localized prostate cancer, or superficial bladder cancer stage 0, from which the subject has not been disease-free for at least 3 years.

e) Known central nervous system involvement by malignancy.

f) Life-threatening active bleeding.

g) Known current drug or alcohol abuse.

h) Apparent active or latent tuberculosis (TB) infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of infectious infiltrate; recent unexplained changes in fever/chill patterns.

i) Respiratory disease requiring continuous supplemental oxygen.

j) Underlying medical conditions that, in the investigator's opinion, will make the administration of ulocuplumab hazardous or obscure the interpretation of toxicity determination or AEs.

k) Active infection (viral, bacterial, or fungal) requiring systemic therapy within 7 days before receiving the first dose of ulocuplumab (prophylactic antibiotic therapy is allowed); Subjects who are judged by the investigator to be clinically well but are obligated to complete a course of antimicrobial therapy would not be considered to have active infection.

l) Any major surgery within 4 weeks of ulocuplumab administration.

m) Inability to tolerate venous access.

n) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

o) Presence of active graft versus host disease -Not applicable as per Protocol Amendment 03

p) Documented pulmonary disease with diffusing capacity of the lungs for carbon monoxide (DLCO) ≤ 65% or FEV1 ≤ 65%

4. Allergies and Adverse Drug Reaction

a) History of Grade 4 hypersensitivity reactions to other monoclonal antibodies, related compounds, or excipients of ulocuplumab.

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

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

3.3.3 Women of Childbearing Potential

Refer to Appendix 5.

3.4 Concomitant Treatments

3.4.1 Permitted Treatments

The following therapies are permitted during the study:

a) Prophylactic antiemetics may be administered at the discretion of the treating physician prior to all doses of ulocuplumab, except the initial infusion of ulocuplumab in Cycle 1.

b) If a subject experiences a Grade 2 infusion reaction with ulocuplumab, the subjects will be required to receive the prophylactic premedications for subsequent infusion of ulocuplumab. The pre-medications including, but not limited to, IV or oral diphenhydramine 50 mg (or

equivalent), acetaminophen 2 x 325 mg orally, and corticosteroids (25 mg of IV hydrocortisone or equivalent) should be administered at least 30 minutes before ulocuplumab administration.

c) Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 20 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

d) Radiation therapy to chloromas allowed, but irradiated lesion may not be used to assess response.

e) Hydroxyurea can be administered up to Day 21 of Cycle 1, if clinically indicated, at the investigator's discretion as per institutional guidelines.

3.4.2 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to ulocuplumab administration in the study are described below. Medications taken within 4 weeks prior to ulocuplumab administration must be recorded on the CRF. Any concomitant medications (prescription, over-the-counter or herbal) administered during the study must be recorded on the CRF.

The following therapies are **prohibited** during the study:

a) Concomitant use of other systemic anti-cancer therapy may not be used while the subject is participating in the study except the follow-up period. Radiation therapy for bone pain will be discussed with the BMS Medical Monitor. No new investigational therapies for any reason shall be initiated while the subject is participating in the study.

b) Subjects taking oral or parenteral corticosteroids must be tapered off this medication prior to the first dose of ulocuplumab and must remain discontinued from all oral and parenteral corticosteroids while participating in the study except the follow-up period (unless used for treatment of infusion reactions, rash or antiemetic prophylaxis or subjects on low-dose corticosteroids [< 20 mg prednisone or equivalent] for chronic conditions. Investigators should discuss individual cases with the BMS Medical Monitor).

c) Concomitant use of medications which may prolong QT intervals are prohibited during Cycle 1 and 2 in subjects participating the serial QTc assessment (Serial PK/ECG Subset). A list of prohibited drugs that prolong QTc will be provided in a separate study guidance document.

3.4.3 Other Restrictions and Precautions

Subjects in the escalation cohort and the expansion cohort may be required to stay in the clinical facility for Day 1 - 15 of Cycle 1. Subjects will be discharged from the clinical facility at the discretion of the investigator based on the available safety data and physical conditions on Day 15. Additionally, subjects may be admitted to the clinical facility for the purpose of including but not limited to study drug administration, sample collection or other study related procedures. Subjects are required to remain in the clinical facility at up to 4 hours after completion of infusion dependent upon presence or absence of infusion reactions from previous ulocuplumab doses.

Subjects should refrain from strenuous physical activity and use of (methyl) xanthines (eg, coffee, tea, cola, chocolate) or alcohol on the days when ECG measurements will be obtained.

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Pregnancy
- Inability to comply with protocol
- Discretion of the investigator
- Disease progression
- New extramedullary disease
- Elective stem cell transplant (SCT)
- Subject is lost to follow up
- Death
- DLT
- AEs which require discontinuation according to Section 4.6.1
- Need for any treatment not allowed by the protocol.

In the case of pregnancy, the investigator must immediately notify Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the Sponsor or designee within 24 hours of awareness of pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF page.

3.6 Post Study Drug Study Follow up

In this study, overall survival (OS) and duration of remission (DoR) is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Subjects who discontinue study drug may continue to be followed.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and

- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents (such as glucose for glucose challenge) given as part of the protocol requirements.

Product description and storage information of study drugs used in this study are described in Table 4-1.

Table 4-1: Study Drugs for CA212016

Product Description and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Ulocuplumab[a] (BMS-936564) Injection, 100 mg/vial (10 mg/mL)	10 mg/ml	IP	Open Label	Single-use 10 mL vial with 100 mg ulocuplumab Colorless, clear to slightly opalescent solution, essentially free of particles	Store at 2°C to 8°C, protect from light and protect from freezing
Cytarabine[b]	Refer to package insert	IP	Open Label	Various packing configurations/Commercial	Refer to label on container or package insert/summary of product characteristics

[a] The clinical label will reflect the product as "BMS-936564" to be linked with the product description.

[b] Cytarabine may be obtained by the investigating site's standard prescribing procedures as allowed.

4.1 Investigational Product

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

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

In this protocol, investigational products are: ulocuplumab and LDAC.

BMS will provide ulocuplumab to all investigating sites as BMS is the manufacturer and provider of the supplies. BMS may also provide LDAC to investigating sites outside of the US. For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label.

4.2 Non-investigational Product

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

In this protocol, non-investigational product is: premedications for infusion reaction (eg, diphenhydramine, acetaminophen and corticosteroids).

The Sponsor will not be providing these medications since they are part of subject's standard of care.

4.3 Storage and Dispensing

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

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

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

Please refer to Section 9.2.2 for guidance on IP records and documentation and Section 4.9 for return and destruction instructions.

Ulocuplumab vials must be stored refrigerated 2°C to 8°C in a tightly closed container and must be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored

in the carton. Once the ulocuplumab injection is transferred to the IV bag, it can be stored for a maximum of 12 hours at room temperature/under ambient light at 15°C to 25°C. If the solution in the IV bag cannot be used for infusion within the 12 hours at room temperature, it must be refrigerated at 2°C to 8°C, not to exceed 12 hours maximum in the refrigerator. The solution is stable for a total storage combination time of 24 hours.

Following transfer to the IV bag, preparation time of dilution to the end time of infusion should not exceed 24 hours as the diluted solution of ulocuplumab once prepared, must be infused within a 24 hour timeframe.

Any temperature deviations from the recommended storage conditions would require the site to contact the Sponsor for further instruction and disposition.

4.4 Study Treatments

See Section 3.4.1 regarding prophylaxis prior to infusion of ulocuplumab.

Escalation Cohort

- Ulocuplumab (600 mg and 800 mg) was administered as a single IV infusion over approximately 60 minutes on Day 1, 8, and 15 of the first 2 cycles and on Day 1 and 8 of each cycle thereafter.
- When administered in combination with LDAC, ulocuplumab was administered prior to the dose of LDAC. It was recommended that LDAC be administered at least 1 hour after completion of ulocuplumab infusion.
- LDAC (low dose cytarabine) (20 mg BID [40 mg total daily dose]) was subcutaneously administered on Day 1 - 10 for all cycles.

Expansion Cohort

- Ulocuplumab (800 mg or 1000 mg) will be administered as a single IV infusion over approximately 60 minutes on Day 1, 8, and 15 of the first 2 cycles and on Day 1 and 8 of each cycle thereafter.
- When administered in combination with LDAC (cytarabine), ulocuplumab will be administered prior to the first dose of LDAC (cytarabine). Cytarabine should be administered at least 1 hour after completion of ulocuplumab infusion.
- LDAC (low dose cytarabine) (20 mg BID [40 mg total daily dose]) will be subcutaneously administered on Day 1 - 10 for all cycles. The second dose of LDAC will be administered per investigator decision, however a minimum of six (6) hours after the first dose LDAC dose is required.
- Subjects in the LDAC only arm will be permitted to add ulocuplumab 800 mg into their treatment regimen if they do not achieve complete remission (CR or complete remission with incomplete blood count recovery [CRi]) confirmed by blast count reduction after 4 treatment cycles or if they relapse after achieving complete remission.

4.4.1 Preparation of Study Drug

Ulocuplumab will be supplied as a single use vial with the 100 mg/vial (10 mg/mL) potency. Allow the appropriate number of ulocuplumab vials to stand at room temperature for approximately 30 minutes before preparation. Dilution of ulocuplumab must be performed using sterile disposable syringes and include 0.9% sodium chloride injection (normal saline). Instructions for dilution of the drug product are provided in the pharmacy manual.

Ulocuplumab must be infused using a volumetric pump through an IV solution infusion set with a sterile, non-pyrogenic, low protein binding 0.2 μm in-line filter. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of approximately 60 minutes. Ulocuplumab must not be administered as an IV push or bolus injection. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain anti-microbial preservatives or bacteriostatic agents. A sufficient excess of drug product is included in each vial to account for withdrawal losses.

Preparation and administration of cytarabine will follow the instruction outlined in the Pharmacy Manual and/or according to the clinical label.

Further details of drug preparation and administration will be described in the pharmacy dosing manual.

4.5 Method of Assigning Subject Identification

After informed consent has been obtained and the subject's initial eligibility is established, the subject must be enrolled into the study by entering information into IWRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Specific instructions for using IWRS will be provided to the investigational site in a separate document. The investigator or designee will be register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Following completion of all Screening Phase evaluations, site personnel will make a call to the IWRS to obtain a treatment assignment. The IWRS will randomly assign subjects to 1:1:1 treatment groups (ulocuplumab 800 mg + LDAC, ulocuplumab 1000 mg + LDAC or LDAC alone). The randomization to the ulocuplumab 1000 mg + LDAC arm may be suspended while the safety of the first 6 patients on this dose is assessed.

Further details of subject enrollment will be described in the procedure manual.

4.6 Selection and Timing of Dose for Each Subject

Subjects were/will be assigned to a dose cohort in the order they enter the study.

Subjects in the escalation cohort received ulocuplumab at 600 or 800 mg administered as a single IV infusion on Day 1, 8 and 15 and LDAC at 20 mg BID (40 mg/day) subcutaneously administered on Day 1 - 10 in Cycle 1 (DLT evaluation period) and Cycle 2. Subjects then received ulocuplumab at 600 or 800 mg on Day 1 and 8 in combination with LDAC at 20 mg BID (40 mg/day) on Day 1 - 10 in Cycle 3 and subsequent cycles. A total of 3 subjects were treated at the dose level of 600 mg. 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 was guided by the number of subjects with DLTs observed during the DLT evaluation period based on the mTPI design (see Section 3.1.1).

Subjects in the expansion cohort will receive ulocuplumab or LDAC alone. Subjects assigned to ulocuplumab arms will receive ulocuplumab 800 mg or ulocuplumab 1000 mg administered as a single IV infusion on Day 1, 8 and 15 and LDAC at 20 mg BID (40 mg/day) subcutaneously administered on Day 1 - 10 in Cycle 1 and Cycle 2. These subjects will then receive ulocuplumab at 800 mg or 1000 mg on Day 1 and 8 in combination with LDAC at 20 mg BID (40 mg/day) on Day 1 - 10 in Cycle 3 and subsequent cycles.

Subjects assigned to the LDAC alone arm will receive 20 mg BID (40 mg/day) on Day 1-10 in every cycle. If ulocuplumab is added to the LDAC alone arm after Cycle 4, the treatment schedule is LDAC 20 mg BID from Day 1 to 10 of each cycle and ulocuplumab 800 mg on day 1, 8 and 15 for the first 2 cycles then ulocuplumab 800 mg on Day 1 and 8 for subsequent cycles. Follow Treatment Procedural Outline (Table 5.1-2).

4.6.1 Discontinuation, Dose Modifications, Infusion Delays and Missed Doses

Subjects will be monitored continuously for AEs while on study therapy. Subjects will be instructed to notify their study physician immediately for any and all AEs. Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests and previous experience with the agent) must be determined. Reasons for discontinuation or delays, the supportive measures taken and the outcome must be documented in the subject's chart and recorded in the CRF.

If the dose of one drug in the regimen (ie, ulocuplumab or LDAC) is delayed or discontinued, after Cycle 1, the treatment with the other drug may continue as scheduled. Subjects experiencing continuous dose delay greater than 56 days in all study drugs (ulocuplumab and LDAC) due to an adverse event(s) related to study treatment must be discontinued from study drug.

4.6.1.1 Treatment Discontinuation Criteria

Subjects will discontinue study treatment upon development of following ulocuplumab-related AEs:

- Prolonged bone marrow suppression (≥ 56 days)
- Grade ≥ 3 infusion reaction
- QTcF ≥ 500 msec confirmed by at least one repeat ECG.

4.6.1.2 Dose Modifications, Infusion Delays and Missed Doses

No subject will be permitted dose modifications of ulocuplumab and LDAC during Cycle 1. After Cycle 1, if the dose of ulocuplumab or LDAC is interrupted or discontinued, the treatment with the other drug may continue as scheduled. Each cycle is 28 days. Missed doses should be skipped, not delayed, if not given within the allowed window. Please consult the BMS Medical Monitor for any questions regarding dose interruption or study therapy discontinuation.

Ulocuplumab:

The study allows dose delays of ulocuplumab but does not allow dose reductions or escalations throughout the treatment period. Dose delays of ulocuplumab are not permitted during Cycle 1.

Criteria to start a new cycle:

- After Cycle 1, every effort should be made to give the first dose of ulocuplumab and LDAC in Cycle 2 within 7 days of the end of the previous cycle in order to maximize dose intensity. Dose delays up to a maximum of 28 days are allowable for grade 3 or 4 non-hematologic toxicities, with resumption of dosing when resolved to grade 1 or less. This does not include situations when the subject's marrow has not yet recovered from effects of chemotherapy from a previous cycle. A dose delay of up to a maximum of 42 days is allowable for prolonged myelosuppression defined by ANC $\leq 500/\mu L$ or platelet count $\leq 10 \times 10^9/L$ in a normal bone marrow with $\leq 5\%$ blasts and no evidence of disease or dysplasia .
- At Cycle 3 and beyond, dose delay for recovery from myelosuppression (or other AE) up to a maximum of 56 days is allowed for grade 3 or 4 non-hematologic toxicities, or prolonged myelosuppression as defined above.

Once a treatment cycle is begun:

- For Cycles 1 and 2, a window of -1 to +3 days is permitted for ulocuplumab administration on Days 8 and 15.
- Beginning with Cycle 3 and beyond, a window of -1 to +7 days is permitted for ulocuplumab administration on Day 8.
- Infusions of ulocuplumab that cannot be administered in that window period will be considered a missed dose, and the subject should come in for their next, regularly scheduled visit relative to Day 1 of the next cycle.

A subject should be discontinued from ulocuplumab if they do not receive a dose within 56 days of the last ulocuplumab dose.

Table 4.6.1.2-1: Dose Delay and Discontinuation Criteria for Ulocuplumab-related Adverse Events

Adverse Event	Action
* Prolonged myelosuppression defined by ANC ≤ 500/μL or platelet count ≤ 10 x 10^9/L in a normal bone marrow with ≤ 5% blasts and no evidence of disease or dysplasia (≥ 56 days) [a] * Grade ≥ 3 infusion reaction * QTcF ≥ 500 msec confirmed by at least one repeat ECG.	Discontinue Ulocuplumab
Grade 4 hematologic toxicity (anemia, neutropenia, leukopenia, or thrombocytopenia) [a]	Hold Ulocuplumab until returns to baseline
≥ Grade 3 non-hematologic adverse event in subjects receiving maximum medical management.	Hold Ulocuplumab until resolves to baseline or ≤ Grade 1

[a] Hematologic parameter changes must be interpreted by the Investigator in the context of the subject's disease status. For example, baseline neutrophil counts may be Grade 3 [⟨≤ 1000 cells/μL] and a decrease to Grade 4 may not be considered clinically significant and would not be considered an adverse event, or may be attributed to the underlying disease. Thus, the risk/benefit of interruption must be assessed by the Investigator for each subject.

LDAC:

After Cycle 1, every effort should be made to give the first dose of ulocuplumab and LDAC in Cycle 2 within 7 days of the end of the previous cycle in order to maximize dose intensity. For subsequent doses, delays in the administration of LDAC and dose adjustments in LDAC are permitted as clinically indicated at the discretion of the investigator.

Continuous Study Treatment Delay ≥ 56 Days:

A study treatment related continuous treatment interruption or delay of ≥ 56 days will result in permanent discontinuation from study treatment, unless the patient is demonstrating clinical benefit, at the discretion of the investigator and after consultation with the BMS Medical Monitor.

4.7 Blinding/Unblinding

Not applicable.

4.8 Treatment Compliance

The investigator or their designated study personnel will maintain a log drug accountability log of all study drug(s) received, dispensed, destroyed, and the amount returned to the Sponsor or supply depot. The investigator and the study personnel will ensure that each subject receives ulocuplumab as well as LDAC (low dose cytarabine).

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

The treatment compliance in this study will be done at the study site where records of compliance will be maintained.

4.9 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the study drug storage manager's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the study drug storage manager's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific timepoints (see Table 5.1-1, Table 5.1-2, and Table 5.1-3.

Every effort should be made to schedule visits within the protocol specified windows. For infusion delays or missed doses, see Section 4.6.1 for administration details.

Laboratory assessments, blood sampling, and vital signs defined in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.5.1-1, and Table 5.5.1-2 should occur within ± 10% of the defined timepoint (eg, a blood sample scheduled for 60 minutes should occur within 6 minutes of the 60-minute mark; eg, a blood sample scheduled for 24 hours should occur within 2.4 hours of the 24-hour mark).

Table 5.1-1: Screening Procedural Outline (CA212016)

Procedure	Screening Visit (Day -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol specific-informed consent is signed.
Medical History	X	Includes demographics, disease diagnosis, prior treatment, any toxicities or allergy related to previous treatments, and prior and concurrent medical conditions.
Baseline signs and symptoms	X	Pre-dose events will be collected.
Inclusion/Exclusion Criteria	X	It must be confirmed that subjects meet all of the inclusion criteria and none of the exclusion criteria prior to dosing on Cycle 1 Day 1.
Safety Assessments		
Physical Examination	X	All abnormal findings are to be collected.
Physical Measurement	X	Height will be measured at screening only. Weight is to be measured at the Screening visit and at each day of ulocuplumab infusion.
Vital Signs	X	Includes body temperature, heart rate, and systolic and diastolic blood pressures. These should be measured after a subject has been rested quietly for at least 5 minutes.
ECOG Performance Status	X	See Appendix 4.
HCT-CI	X	See Appendix 6.
12-lead Electrocardiogram (ECG)	X	Must be performed using QTc (Fridericia correction).
Serology	X	Serum for Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B core antibody (In the case of positive Hepatitis B core antibody, if Hepatitis B DNA by quantitative PCR is undetectable, subjects are eligible), HIV antibody.
Hematology	X	Laboratory results must be reviewed before the first dose of ulocuplumab. Samples may be drawn up to 72 hours before infusion to meet this requirement. Please refer to Section 5.3.2.
Chemistry	X	Laboratory results must be reviewed before the first dose of ulocuplumab. Samples may be drawn up to 72 hours before infusion to meet this requirement. Please refer to Section 5.3.2.
Urinalysis	X	Laboratory results must be reviewed before the first dose of ulocuplumab. Samples may be collected up to 72 hours before infusion to meet this requirement Please refer to Section 5.3.2.

Table 5.1-1: Screening Procedural Outline (CA212016)

Procedure	Screening Visit (Day -28 to -1)	Notes
Pregnancy Test	X	WOCBP only. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Pregnancy test must be negative to continue.
Concomitant medications	X	Medications taken within 28 days prior to study drug administration and concurrent medications must be recorded on the CRF. Includes medical treatment procedures also.
Adverse Event Reporting		
Serious Adverse Events Assessment	X	All serious adverse events (SAEs) must be collected from the date of subject's written consent until 30 days after discontinuation of dosing. All SAEs must be collected that occur within 30 days of the last visit for screen failures.
Efficacy Assessments		
Bone marrow aspirate/biopsy	X	Baseline bone marrow aspirate/biopsy (local lab) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of ulocuplumab need not be repeated. Report will be sent to BMS.
Diagnostic testing for extramedullary disease	X	Testing for extramedullary disease as part of subject's routine care, if clinically indicated.
RBC transfusion dependency	X	RBC transfusion taken within 28 days prior to study drug administration must be recorded on the CRF. The threshold for transfusion will be determined at the investigator's discretion.
[redacted]		
Other Assessments		
Central Lab Cytogenetic testing	X	Bone marrow aspirate will be collected (karyotype).
C-Reactive Protein (CRP)	X	May be obtained during screening or prior to first dose.

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
Other Assessments												
C-Reactive Protein	X											CRP must be obtained prior to first dose if CRP has not been collected at screening.
Safety Assessments												
Physical Examination	X		X		X	X					X	All abnormal findings and any new or worsening signs and/or symptoms are to be recorded as AEs after study drug administration.
Physical Measurement	X		X		X	X		X			X	Weight only.
Vital Signs	X		X		X	X		X			X	Includes body temperature, heart rate, and systolic and diastolic blood pressures. These should be measured after a subject has been rested quietly for at least 5 minutes. Vital signs will be obtained with the following schedule: Cycle 1: before ulocuplumab infusion, 15 and 30 minutes during the infusion, at the completion of infusion, at 60 minutes after the completion of infusion on the day of ulocuplumab infusion. Cycle 2 and subsequent cycles: before ulocuplumab infusion and at the

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
												completion of infusion on the day of ulocuplumab infusion.
ECOG Performance Status	X					X					X	See Appendix 4.
HCT-CI											X	See Appendix 6.
12-lead ECG	X					X					X	For all subjects, for Day 1 of each cycle, ECG tests will be performed at pre-dose. On Day 1 of Cycle 1, it will also be performed at the completion of ulocuplumab infusion. For subjects in the Serial PK/ECG Subset, see Table 5.5.1-1 for ECG/holter monitor schedule for Cycle 1 and 2.

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
Hematology	X		X		X	X		X			X	Laboratory results must be reviewed before dosing. Samples may be collected up to 72 hours before infusion of ulocuplumab Hematology assessment includes complete blood count, in addition to the differential that enumerates absolute counts of circulating tumor cells (if any), neutrophils, lymphocytes, monocytes, basophils, eosinophils. Absolute counts and/or percentages may be reported. Lab tests associated with efficacy assessments may be conducted at appropriate timings as needed. Please refer to Section 5.3.2
Chemistry	X		X		X	X					X	Laboratory results must be reviewed before dosing. Samples may be collected up to 72 hours before infusion of ulocuplumab. Please refer to Section 5.3.2
Urinalysis	X					X					X	Laboratory results must be reviewed before dosing. Samples may be collected up to 72 hours before infusion of ulocuplumab. Please refer to Section 5.3.2
Pregnancy Test	X					X					X	WOCBP only.

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
												Serum or urine pregnancy testing immediately before day 1 infusion. Minimally, monthly pregnancy testing is required. During dose delays greater than 4 weeks, pregnancy testing must be completed within 30 days from the date of the last pregnancy test until dosing resumes.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	Concurrent medications must be recorded on the CRF during the study. Includes medical treatment procedures also.
Adverse Event Reporting												
SAEs	X	X	X	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 30 days after discontinuation of dosing.
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	All abnormal findings and any new or worsening signs and/or symptoms are to be recorded as AEs after study drug administration. All AEs must be collected from the initiation of study drug until 30 days after the end of treatment. Study drug-related AEs that are reported/identified during the follow up period should be followed to resolution,

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
												stabilization, or initiation of new therapy or until deemed irreversible.
PK Assessments												
Serum sample for PK												Applies to Ulocuplumab/LDAC combination arms only See Table 5.5.1-1 and Table 5.5.1-2
Immunogenicity Assessments												
Serum sample for immunogenicity												Applies to Ulocuplumab/LDAC combination arms only See Table 5.5.1-1 and Table 5.5.1-2
Efficacy Assessments												
Leukemia response assessment										X	X	Leukemia response assessment will be evaluated for each cycle using the AML IWG 2003. The results of the response assessments must be reviewed and documented before the first dose of the next cycle.

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
Bone marrow aspirate/biopsy										X	X	The results of the local lab bone marrow aspirate (or biopsy) done as part of routine care will be sent to BMS. Bone marrow aspirate is sufficient for the leukemia response evaluation. The marrow must be of adequate recovery and cellularity for evaluation. If the bone marrow has not yet recovered, repeat the bone marrow until a leukemia response can be determined. The next cycle of treatment is delayed until the marrow is of adequate recovery and cellularity for a response assessment to be completed.
Diagnostic testing for extramedullary disease										X	X	Testing for extramedullary disease as part of subject's routine care, if clinically indicated.
RBC transfusion requirements	X		X		X			X			X	The threshold for transfusion will be determined at the investigator's discretion.
[redacted]												

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
[redacted]												

Table 5.1-2: Treatment Procedural Outline (CA212016)

Procedure[a]	Treatment (28 days/cycle)										EOT[b]	Notes
	Cycle 1-2[c]					Cycle 3 and subsequent cycles[c]				All Cycles		
	D1[d]	D 2-7	D 8[e]	D 9-10	D 15[e f]	D1[d]	D 2-7	D8[g h]	D 9-10	D 24-28[i]		
Clinical Drug Supplies												
Ulocuplumab infusion	X		X		X	X		X				If a subject experiences a Grade 2 infusion reaction with ulocuplumab, the subject will be required to receive prophylactic premedications for subsequent infusions of ulocuplumab. The pre-medications include, but not limited to, diphenhydramine, acetaminophen, and low-dose corticosteroids. See Sections 4.4 and 4.6.
Cytarabine administration	X	X	X	X		X	X	X	X			Cytarabine is administered on Day 1 - 10 in each cycle. See Sections 4.4 and 4.6.
Study drug withdrawal/study withdrawal procedures											X	End of Treatment visit should be performed any time a subject discontinues study treatment.

[a] All on-treatment sample collections/assessments are to be done prior to dosing unless otherwise indicated.

[b] The end of treatment visit should be performed any time a subject discontinues study treatment.

[c] Subjects who discontinue ulocuplumab treatment for any reasons will be followed for 30 day after the end of treatment visit.

[d] A window of ± 1 day is permitted.

[e] For Cycles 1 and 2, a window of -1/+3 days is permitted for Days 8 and 15.

[f] D15 does not apply to the LDAC-only arm.

[g] Beginning with Cycle 3, a window of -1/+7 days is permitted for Day 8.

[h] If ulocuplumab is not administered on Day 8 of Cycle 3 and/or subsequent cycles due to a dose delay, study treatment should begin with the next cycle and Day 1 procedures should be completed.

[i] Efficacy assessment and associated testing will be conducted at or after Day 24 of a previous cycle prior to Day 1 of each cycle except Cycle 1. Evaluations during dose delays may be conducted up to 5 days prior to Day 1 of the next cycle start after the dose delay.

[j] Collections at Cycle 3 and every 3 cycles thereafter.

Abbreviations: EOT = End of Treatment; F/U = Follow-up

Table 5.1-3: Follow-up Assessments (CA212016)

Procedure	X, Follow-up Visit - 30 days[a,b]	S, Survival Follow-up Visits[c]	Notes
Safety Assessments			
Physical Examination	X		All abnormal findings and any new or worsening signs and/or symptoms are to be recorded as AEs after study drug administration.
Physical Measurement	X		Weight only.
Vital Signs	X		Includes body temperature, heart rate, and systolic and diastolic blood pressures. These should be measured after a subject has been rested quietly for at least 5 minutes.
ECOG Performance Status	X		See Appendix 4.
12-lead ECG	X		
Hematology	X		Please refer to Section 5.3.2
Chemistry	X		Please refer to Section 5.3.2
Urinalysis	X		Please refer to Section 5.3.2
Pregnancy Test	X		WOCBP only.
Concomitant medications	X		Concurrent medications must be recorded on the CRF during the study. Includes medical treatment procedures also.
Adverse Event Reporting			
SAEs	X		All SAEs must be collected from the date of subject's written consent until 30 days after discontinuation of dosing.
Adverse Events	X		All abnormal findings and any new or worsening signs and/or symptoms are to be recorded as AEs after study drug administration. All AEs must be collected from the initiation of study drug until 30 days after the end of treatment.

Table 5.1-3: Follow-up Assessments (CA212016)

Procedure	X, Follow-up Visit - 30 days[a,b]	S, Survival Follow-up Visits[c]	Notes
			Study drug-related AEs that are reported/identified during the follow up period should be followed to resolution, stabilization, or initiation of new therapy or until deemed irreversible.
PK Assessments			
Serum sample for PK	X		Applies to Ulocuplumab/LDAC combination arms only See Table 5.5.1-1
Immunogenicity Assessments			
Serum sample for immunogenicity	X		Applies to Ulocuplumab/LDAC combination arms only See Table 5.5.1-1
Efficacy Assessments			
Bone marrow aspirate/biopsy	X		The results of the local lab bone marrow aspirate (or biopsy) done as part of routine care will be sent to BMS. Bone marrow aspirate is sufficient for the leukemia response evaluation. The marrow must be of adequate recovery and cellularity for evaluation. If the bone marrow has not yet recovered, repeat the bone marrow until a leukemia response can be determined. The next cycle of treatment is delayed until the marrow is of adequate recovery and cellularity for a response assessment to be completed.
Diagnostic testing for extramedullary disease	X		Testing for extramedullary disease as part of subject's routine care, if clinically indicated.
RBC transfusion requirements	X		The threshold for transfusion will be determined at the investigator's discretion.
[redacted]			
[redacted]			

Table 5.1-3: Follow-up Assessments (CA212016)

Procedure	X, Follow-up Visit - 30 days[a,b]	S, Survival Follow-up Visits[c]	Notes
[redacted]			
Subject Status			
Survival Status	X	X	Every 3 months after X01; may be accomplished by visit or phone contact , to update survival information and assess subsequent anti-cancer therapy

[a] Subjects who discontinue ulocuplumab combination or LDAC alone treatment for any reason will be followed for 30 day after the end of treatment visit.

[b] A window of ± 7 days is permitted.

[c] A window of ± 30 days is permitted.

[redacted]

The end of treatment visit should be performed on the day a decision is made to discontinue study treatment. In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low:

1. PK and RO Sampling
2. Safety (ECG)
3. Safety (vital signs)
4. Safety (clinical labs).

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed as it represents the subject's most current, clinical state.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale for recording height and body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises. The site will have a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will have the proper equipment for the infusion of ulocuplumab including an infusion pump.

The site will also provide premedication for infusion reaction.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), investigator brochure and procedure manuals. Case report forms (electronic or hard copy) will be provided by BMS. BMS/The Central Laboratory will provide labels and tubes for the collection of blood samples for PK and immunogenicity analysis.

5.3 Safety Assessments

The study is divided into periods with associated evaluations and procedures that must be performed at specific timepoints. The Time and Events Schedules (Table 5.1-1, Table 5.1-2, and Table 5.1-3) summarizes the frequency and timing of these evaluations and procedures.

The following safety assessments will be performed during the study for all subjects: vital sign measurements, clinical laboratory tests, bone marrow tests, ECOG performance status evaluations (Appendix 4), physical examinations/measurements, ECGs (12-lead), concomitant medications, transfusions, and the incidence and severity of AEs.

The incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance.

Subjects will be evaluated for safety if they have received at least 1 dose of study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Follow-up visit X01, Table 5.1-3), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls/emails to assess the subject's status are acceptable.

5.3.1 Evaluation and Reporting of Dose Limiting Toxicity (DLT)

DLT will be determined based on the incidence and intensity of AEs occurring in Cycle 1 using NCI CTCAE v4.03. DLT(s) will be defined as any of the following events which are attributed (ie, judged to be related) to the ulocuplumab. AEs that are judged by the investigator to be solely attributed to cytarabine (based upon clinical experience and the known toxicities of these agents), will not be considered DLTs. AEs should be evaluated carefully by the investigator prior to attribution. AEs may be attributed to ulocuplumab if, in the judgment of the investigator, the nature, severity, or timing is unexpected from LDAC (cytarabine). If the events listed below occur, these events will be discussed by the investigator and the BMS Medical Monitor to determine whether they qualify as DLT or not considering its clinical significance. Study drugs (ulocuplumab and LDAC (cytarabine)) will be permanently discontinued for any subject that experiences a DLT.

DLT is defined as:

- Any ulocuplumab related grade ≥ 3 nonhematologic toxicity not due to the underlying disease occurring during Cycle 1.
- Marrow that does not adequately recover within 8 weeks from the last study drug administration (< 10% cellularity with < 10% blasts) will be considered a hematologic DLT if related to ulocuplumab.
- Any ulocuplumab related grade 4 (life-threatening) hematologic toxicity lasting > 14 days.

The following will <u>not</u> be considered a DLT:

- Grade 3 nausea or vomiting that are controllable with medications
- Grade 3 neutropenic fevers or infections
- Grade ≥ 3 tumor lysis syndrome
- Grade ≥ 3 metabolic derangements attributed to antifungal medications or tumor lysis that corrected with IV or oral supplementation
- Grade 3 stomatitis that resolves within 7 days of discontinuation of chemotherapy
- Grade ≥ 3 hypercholesterolemia
- Grade 3 hyperbilirubinemia or transaminitis that resolves to below grade 2 within 14 days
- Grade 3 infusion reactions.

Subjects will be considered to have completed a DLT assessment period if they complete all doses of ulocuplumab and cytarabine for Cycle 1 (28 days). This does not apply to subjects who experience DLTs.

5.3.2 Laboratory Test Assessments

A local laboratory will perform the analyses including C-Reactive Protein testing and will provide reference ranges for these tests.

Results of local clinical laboratory tests must be reviewed prior to infusion.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count (and differential)

- Automated differentials are acceptable, absolute counts reported and/or percentages of circulating tumor cells (if any), neutrophils, lymphocytes, monocytes, basophils, eosinophils.

Platelet count
Blast percentage

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase
Creatinine
Blood Urea Nitrogen or Urea
Uric acid
Lipase
Amylase
Glucose
Total Protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Creatine kinase

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase
Microscopic examination of the sediment including WBC/high power field (HPF), red blood cell (RBC)/HPF if blood, protein or leukocytes esterase are positive on the dipstick
Pregnancy Test (WOCBP only); urinalysis or serum

Serology

Hepatitis C antibody
Hepatitis B surface antigen
Hepatitis B core antibody
HIV antibody

Other:
C-Reactive Protein

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3, Laboratory Test Abnormalities).

5.3.3 Other Assessments

- ECOG assessment (Appendix 4)
- HCT-CI assessment (Appendix 6)
- Physical Examination/Measurement
- Vital Signs
- ECG-safety ECGs will be done for all subjects at screening, during the treatment period and during follow-up as indicated in Table 5.1-1, Table 5.1-2, and Table 5.1-3 . Serial ECGs will be obtained only from a subset of subjects in the expansion cohort (a minimum of 15 subjects per dose level, Serial PK/ECG subset) as indicated in Table 5.5.1-1.
- Concomitant Medications including Medical Treatment Procedures.

5.3.4 Additional Data to be Collected during Trial

Reasons for early discontinuation of any treatment cycle will be collected. This may include but not be limited to progression of cytopenias, lymphadenopathy, organomegaly, fever, weight loss, night sweats, fatigue, etc.

5.3.5 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

Efficacy assessments will be determined by changes in bone marrow aspirate/biopsy, hematological laboratory tests, red blood cell transfusion dependency, and assessments for extramedullary disease (if applicable). Leukemia response assessment will be evaluated using AML IWG 2003 (Appendix 1).

The Time and Events Schedules (Table 5.1-1, Table 5.1-2, and Table 5.1-3) summarizes the frequency and timing of efficacy measurements.

Primary efficacy analyses will be based on the best overall response.

5.4.2 Secondary Efficacy Assessments

Duration of remission (DoR) and overall survival are secondary endpoints. Refer to Section 8.3 for the definition of these endpoints. For OS, every effort should be made to collect survival date on all randomized subjects including subjects who withdraw from treatment for any reason, who

are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported every date collected in this study representing a date of subject contact will be used in determining the subject's last known alive date.

5.5 Pharmacokinetic Assessments

Blood samples for PK can be obtained from a peripheral IV site or central venous access device. PK samples cannot be obtained from the same line used for drug administration or from an IV site above the site used for drug administration. When the drug is infused through a multi-lumen catheter, the alternate lumen should not be used for sampling due to the risk of drug contamination. All post-infusion samples must be collected within ± 10% of the defined timepoints in Table 5.5.1-1 and except 1.5 h samples after starting infusion which must be collected within 15 minutes of the timepoint. Further details of blood collection and processing will be provided to the site in the procedure manual.

PK samples are collected from subjects in the ulocuplumab/LDAC combination arms only. Subjects in the LDAC alone arm, who add ulocuplumab to their treatment regimen are not required to participate in PK measurements.

5.5.1 Pharmacokinetics Collection and Processing and ECG Measurements

Serial blood samples will be collected from the dose escalation cohort. Serial blood samples and time-matched ECGs will be collected from a subset of subjects in the expansion cohort (a minimum of 15 subjects per dose level, Serial PK/ECG Subset) whereas sparse blood samples will be collected in the remaining subjects (sparse sampling subset). Serum for all ADA samples will be collected within 30 minutes before dosing.

Table 5.5.1-1 and Table 5.5.1-2 list the sampling schedule to be followed for the assessment of PK, ECG, ADA and RO. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.5.1-1: Ulocuplumab PK and RO Sampling Schedule and ECG Measurements (Escalation Cohort and Expansion Cohort, Serial PK/ECG Subset)

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample	RO Sample	ADA Sample	ECG[a]
Cycle 1, Day 1	-1.0	-01:00				X
	0 (pre-dose)	00:00	X	X	X	X[b]
	1.0 (end of infusion)[c]	01:00	X	X		
	1.5	01:30	X			X[b]
	2.0	02:00	X			
	3.0	03:00	X			X[b]
	5.0	05:00	X			
Cycle 1, Day 2	24	24:00	X			
Cycle 1, Day 3	48	48:00	X			
Cycle 1, Day 4	72	72:00	X			
Cycle 1, Day 8	0 (pre-dose)	00:00	X	X		
	1.0 (end of infusion)[c]	01:00	X	X		
Cycle 1, Day 15	0 (pre-dose)	00:00	X	X	X	
	1.0 (end of infusion)[c]	01:00	X	X		
Cycle 2, Day 1	0 (pre-dose)	00:00	X	X	X	
	1.0 (end of infusion)[c]	01:00	X	X		
Cycle 2, Day 8	0 (pre-dose)	00:00	X	X		
	1.0 (end of infusion)[c]	01:00	X	X		
Cycle 2, Day 15	0 (pre-dose)	00:00	X	X		X[b]
	1.0 (end of infusion)[c]	01:00	X	X		
	1.5	01:30	X			X[b]
	3.0	03:00	X			X[b]

Table 5.5.1-1: Ulocuplumab PK and RO Sampling Schedule and ECG Measurements (Escalation Cohort and Expansion Cohort, Serial PK/ECG Subset)

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample	RO Sample	ADA Sample	ECG[a]
Cycle 3-5, Day 1[d]	0 (pre-dose)	00:00	X	X	X	
	1.0 (end of infusion)[c]	01:00	X	X		
Cycle 3-5, Day 8[d]	0 (pre-dose)	00:00	X	X		
	1.0 (end of infusion)[c]	01:00	X	X		
Every 4 Cycles after 5, Day 1	0 (pre-dose)	00:00	X		X	
End of Treatment			X		X	
Follow-up[e]			X		X	

[a] ECG only for subjects in expansion cohort Serial PK/ECG Subset

[b] 12-lead ECGs will be extracted from the Holter recorded flashcards in triplicate within a 10-minute window ending prior to the nominal ECG collection time and before PK draws

[c] If infusion has not completed at 1 hour, then draw PK sample immediately after the infusion ends and record time accurately.

[d] The Day 1 and Day 8 pre-dose and end of infusion samples to be collected at Cycle 3 and every cycle thereafter until Cycle 5.

[e] Follow-up visit should occur no less than 30 days after the end of treatment visit

Table 5.5.1-2: Ulocuplumab PK and RO Sampling Schedule (Expansion Cohort, Sparse Sampling Subset)

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample	RO Sample	ADA Sample
Cycle 1, Day 1	0 (pre-dose)	00:00	X	X	X
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 1, Day 8	0 (pre-dose)	00:00	X	X	
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 1, Day 15	0 (pre-dose)	00:00	X	X	X
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 2, Day 1	0 (pre-dose)	00:00	X	X	X
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 2, Day 8	0 (pre-dose)	00:00	X	X	
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 2, Day 15	0 (pre-dose)	00:00	X	X	
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 3-5, Day 1[b]	0 (pre-dose)	00:00	X	X	X
	1.0 (end of infusion)[a]	01:00	X	X	
Cycle 3-5, Day 8[b]	0 (pre-dose)	00:00	X	X	
	1.0 (end of infusion)[a]	01:00	X	X	
Every 4 Cycles after Cycle 5, Day 1	0 (pre-dose)	00:00	X		X
End of Treatment			X		X
Follow-up[c]			X		X

[a] If infusion has not completed at 1 hour, then draw PK sample immediately after the infusion ends and record time accurately.

[b] The Day 1 and Day 8 pre-dose and end of infusion samples to be collected at Cycle 3 and every cycle thereafter until Cycle 5.

[c] Follow-up visit should occur no less than 30 days after the end of treatment visit.

5.5.2 Pharmacokinetic Sample Analysis

Serum samples will be analyzed for ulocuplumab by a validated immunoassay.

The PK and potential covariate(s) data may be combined with data from other studies.

5.5.3 Labeling and Shipping of Biological Samples

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

5.6 ECG Assessments

Safety ECGs will be done for all subjects at screening, during the treatment period and during follow-up as indicated in Table 5.1-1, Table 5.1-2, and Table 5.1-3. All required safety ECGs will be performed on 12-lead ECG equipment used by the sites, per ECG central vendor guidelines.

Serial ECGs will be obtained only from a subset of subjects in the expansion cohort (a minimum of 15 subjects per dose level, Serial PK/ECG Subset) as indicated in Table 5.5.1-1 and should be obtained at each time point listed.

The subjects must be placed in a supine position for 5 to 10 minutes prior to the start of the ECG recording for both safety and serial ECGs. The recorded QTc interval will be measured with Fridericia's correction (QTcF).

All required serial ECGs will be collected on ECG holter monitor equipment provided by the ECG central vendor. The timing of the ECG data collected on the holter monitor is critical to the endpoint of the study and must be performed according the central vendor guidelines. The serial 12-lead ECGs will be extracted from the Holter recorded flashcards in triplicate within a 10-minute window ending prior to the nominal ECG collection time and before PK draws. The serial ECGs will be assessed by the ECG vendor.

The investigative site should document any deviations from the protocol or procedures related to ECG collection or serum sampling. Accurate documentation will lead to proper accounting of the cumulative data and correct final analysis.

5.8 Immunogenicity Assessments

Samples for the analysis of anti-drug antibodies (ADA) to ulocuplumab (immunogenicity) will be collected at pre-dose in all subjects according to the schedules in Table 5.5.1-1 and Table 5.5.1-2. Additional sample handling, labeling, and shipping details will be provided to the site in the procedure manual. Serum samples will be analyzed by a validated immunogenicity assay. Samples are always to be collected prior to the administration of study medication.

ADA samples are collected from subjects in the ulocuplumab/LDAC combination arms only. Subjects in the LDAC alone arm, who add ulocuplumab to their treatment regimen are not required to participate in ADA measurements.

5.9 Outcomes Research Assessments

Not applicable.

5.10 Other Assessments

5.10.1 Additional Research

This protocol will include residual sample storage for additional research (AR).

For All US sites:

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

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

For non-US Sites

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

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

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

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

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

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

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

Table 5.10.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Serum for Pharmacokinetics	All samples
Bone Marrow Aspirate	All samples
Peripheral blood collections (including serum and plasma)	All samples

5.10.2 Cytogenetic and Molecular Assessments

A central laboratory will perform the following:

Baseline cytogenetic testing - bone marrow aspirate chromosome analysis and, if applicable, AML prognostic panel

5.11 Results of Central Assessments

Results of PK and immunogenicity assessments will be provided in aggregate after the end of the study as needed. All serial ECGs will be transmitted to a central laboratory for measurement of intervals and classification of ECG abnormalities.

6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

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

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject or a partner of a male subject is pregnant or may have been pregnant at the time of study exposure, including 78 days (5 half-live s of study drug plus duration of ovulatory cycle) for a female subject and 138 days (5 half-lives of study drug plus duration of sperm turnover) for a partner of a male subject after product administration, the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with Sponsor/designee, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor or designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

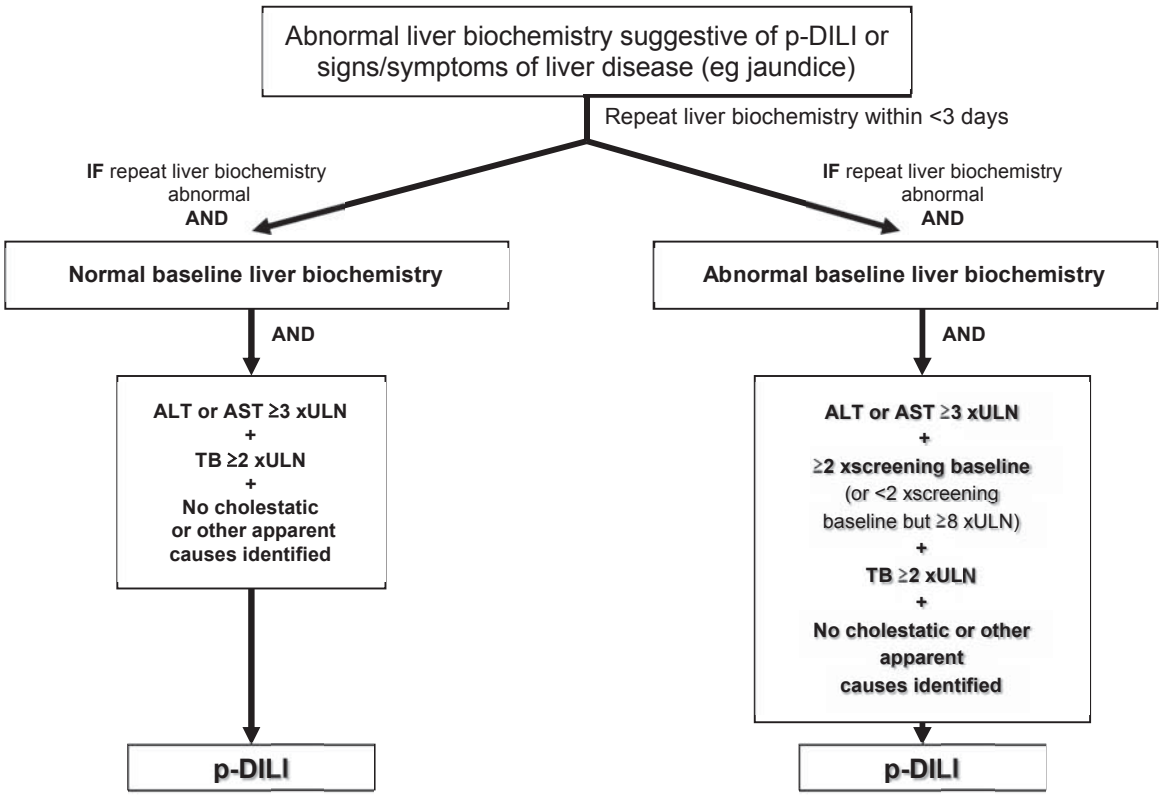
6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

The criteria for identifying p-DILI events depend on whether the subject's baseline liver biochemistry is normal or abnormal (see Figure 6.6-1).

Potential drug induced liver injury is defined as:

Figure 6.6-1: Algorithm for p-DILI identification and mandatory SAE reporting in subjects with (i) normal baseline liver biochemistry, and (ii) abnormal baseline liver biochemistry



6.7 Other Safety Considerations

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

Since ulocuplumab contains only human protein sequences, it is unlikely to be immunogenic and to induce infusion or hypersensitivity reactions. Since this antibody specifically binds to CXCR4, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo or hypertension, bronchospasm, or other symptoms.

As of the 17-Feb-2014 cut-off date, infusion reactions have been reported in 1 AML subject, 3 CLL subjects and 1 DLBCL subject out of the 86 treated subjects in the CA212001 study and 2 myeloma subjects out of the 42 treated subjects in the CA212002 study.

Prophylactic premedication may be given any time after the first dose of Cycle 1. However, if a subject experiences a Grade 2 infusion reaction, the subject will be required to receive prophylactic premedication for subsequent infusions of ulocuplumab (Section 3.4.1).

Infusion reactions should be graded according to the NCI CTCAE v4.03 guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. Information on prophylactic premedications is provided in Section 3.4.1.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti inflammatory drugs (NSAIDs), narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the ulocuplumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further ulocuplumab will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), paracetamol (acetaminophen) and/or corticosteroids should be administered at least 30 minutes before additional ulocuplumab administration. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of ulocuplumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The

subject should be monitored until the investigator is comfortable that the symptoms will not recur. Ulocuplumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An independent data monitoring committee (DMC) will be constituted for review of safety information and assessment of overall benefit/risk balance in this study. Specific data to be reviewed and timing of the reviews by the DMC will be described in a DMC Charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The size of the study is not based on testing a formal statistical hypothesis. The Escalation Cohort is a Phase 1 safety phase 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 in this cohort, assuming 600 mg and 800 mg are explored. For the Expansion Cohort (Phase 2), 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=CR+CRi). A response rate of 0.6 will be estimated with the following 95% exact confidence interval (CI): 0.43 - 0.75. If the response rate is 0.45, then the associated 95% CI will be 0.29 - 0.62.

8.2 Populations for Analyses

The following populations will be defined for each cohort.

- *All Enrolled Subjects:* All subjects who signed an informed consent form. 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. This dataset will be used for baseline and efficacy analyses.
- *All Treated Subjects:* All subjects who received at least one dose of study medication (ulocuplumab in the combination arm and LDAC in the LDAC only arm). This dataset will be used for safety analyses (as well as some efficacy analyses).
- *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.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

- Phase 1 (escalation cohort): DLTs in Cycle 1, and AEs, ≥ Grade 3 AEs, AEs leading to discontinuation, SAEs, deaths and laboratory abnormalities in combination therapy during the Treatment period plus 30 days of follow-up will be the primary endpoints for this study. AEs will be graded according to NCI CTCAE v4.03
- Phase 2 (expansion cohort): Investigator will assess best overall response. The primary endpoint will be based on the 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). The primary analysis will be conducted after all patients had an opportunity for 6 months of follow-up. Please refer to Appendix 1 for AML response criteria.

8.3.2 Secondary Endpoint(s)

- Phase 1 (escalation cohort): Investigator assessed best overall response prior to the initiation of any alternative therapy. Please refer to Appendix 1 for AML response criteria.
- Phase 2 (expansion cohort): 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 will be the primary endpoints for this study. AEs will be graded according to NCI CTCAE v4.03.
- ADA positive for ulocuplumab.
- PK parameters will be determined for subjects in both escalation and expansion cohorts, 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 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.

- In Phase 2 (expansion cohort): To assess rates of Overall Remission (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.
- In Phase 2 (expansion cohort): To assess efficacy (in terms of rates of CR/CRi and OR and duration of remission, 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.
- Duration of remission (DoR) is defined as the time from the date of first documented CR or 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.
- 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 hear rate correction.) The schedule for ECGs is given in Table 5.5.1-1 (PK, RO, ADA, and ECG Sampling).
- Overall survival (OS) will also be summarized. OS is defined as 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.

[redacted]

8.4 Analyses

The following will be analyzed separately by cohort, and by treatment group within the expansion cohort.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race and ECOG status will be tabulated. Summary statistics for age, body weight, height and body mass index will be tabulated.

8.4.2 Efficacy Analyses

Individual tumor responses will be listed by treatment and study day. Bone marrow blast and its percent change from baseline will be listed.

In addition, for the expansion cohort, best overall response prior to the initiation of any alternative therapy (including any subsequent ulocuplumab 800 mg for subjects in the LDAC alone arm) will be tabulated. 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. The combined rate of subjects with responses of either CR or CRi or PR will similarly be summarized.

OS and DoR will be summarized descriptively using Kaplan-Meier methodology. Median values of OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method considering a log-log transformation, will be calculated.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs, clinical laboratory test results and any significant physical examination findings will be listed and summarized by treatment. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. To assess the effects of ulocuplumab on heart rate, PR, QRS, QT, QTcF, and ΔQTcF intervals the frequency distribution for maximum QTcF, PR, QRS and the maximum ΔQTcF will be tabulated. For QTcF a linear regression of ΔQTcF on drug concentration will be estimated. Summary statistics will be tabulated for all ECG parameters and changes from baseline. The plots of mean and mean changes from baseline versus time or ulocuplumab concentration may be provided. A two-sided 90% confidence interval will be constructed for the population mean of ΔQTcF at each time point.

8.4.4 Immunogenicity Analyses

Immunogenicity status will be reported relative to baseline as ADA negative, ADA positive, and positive baseline. Listings for ADA positive response will be provided by treatment.

8.4.5 Pharmacokinetic Analyses and Receptor Occupancy

Summary statistics will be tabulated for the PK parameters and RO (expansion cohort only) listed in Section 8.3.2 by treatment and study day. For PK, geometric means and coefficients of variation will be presented for Cmax, AUC and CL. Medians, minimum, and maximum will be presented for Tmax. Means and standard deviations will be provided for the remaining PK parameters. Individual as well as mean concentration-time plots will be depicted.

The distribution of Ctrough concentrations will be summarized using descriptive statistics by treatment and study day. To assess the attainment of steady state, geometric mean Ctrough values will be plotted by treatment and study day.

Changes of CXCR4 RO is related to the dose and exposure of ulocuplumab. The association between the percent of RO and ulocuplumab serum concentration in peripheral blood and, when possible, bone marrow will be explored.

8.4.6 ECG Analyses

Triplicate measurements of each serial ECG will be used to obtain an average value for each time point. These averages will be used in the listings and statistical analyses. Baseline will be defined as the time point prior to dosing on the first day of Cycle 1. Summary statistics (n, mean, standard deviation of the mean, minimum and maximum) will be provided for all ECG intervals (QT, QTcF,

QTcB, QRS, PR) and for heart rate and changes relative to baseline in ECG intervals and heart rate, per day and time point.

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 msecs, 481- 500 msecs, > 500 msecs) for QTcF and (≤ 30 msec, 31- 60 msec, > 60 msec) for ΔQTcF. ECG analyses will be conducted on the ECG evaluable population. These analyses will be summarized separately for each cohort.

8.4.8 Outcomes Research Analyses

Not applicable.

8.4.9 Other Analyses

HCT-CI scores will be summarized at baseline and at end of treatment.

Cytogenetic and molecular results will be summarized at baseline only.

8.5 Interim Analyses

For the dose expansion cohort, an interim assessment of safety will be assessed by Sponsor or designee on the first 6 patients treated on the 1000 mg ulocuplumab/LDAC combination arm. These must have had an opportunity for at least 28 days of follow-up. The review will be based all available safety data including DLTs reported during the first 28 days of follow-up. Randomization to the 1000 mg ulocuplumab combination arm will be suspended until the safety review is complete. Randomization to the other 2 arms will continue on a 1:1 basis until a decision is reached to resume randomization to all 3 arms.

In addition, an interim analysis of efficacy and safety will be conducted when 60 patients (i.e., 50% of the sample size) will have had an opportunity for 2 months of treatment and follow-up.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Source documents are defined as follows: screening log, subject identification code sheet, medical records, written informed consent, and study drug management sheets. Certain CRF pages and/or electronic files may serve as the source documents: such as the investigator assessment of efficacy.

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

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

9.1.2.1 Source Documentation

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

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

Records for IP must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be

explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

BMS and the investigator will maintain an original and a copy of the signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

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

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

9.3 Clinical Study Report and Publications

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

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

- Subject recruitment (eg, among the top quartile of enrollers)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS or designee. Any publications or abstracts arising from this study must adhere to BMS's publication requirements set forth in the clinical trial agreement (CTA) governing Investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AML IWG 2003	2003 International Working Group Response Criteria for AML
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BID	twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
CDC	complement-dependent cytotoxicity activity
CLL	chronic lymphocytic leukemia
CLT	total body clearance
Cmax	maximum observed concentration
Cmin	trough observed concentration
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CRF	case report form
CRP	C-reactive protein
Ctrough	Trough observed plasma concentration
CXCL12	C-X-C motif ligand 12
CXCR4	C-X-C chemokine receptor type 4
DILI	drug induced liver injury
DLBCL	diffuse large B-cell lymphoma

Term	Definition
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FL	follicular lymphoma
FSH	follicle stimulating hormone
GCP	good clinical practice
HCT-CI	hematopoietic cell transplant-comorbidity index
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgG4	immunoglobulin G4
IL	interleukin
IMP	investigational medicinal products
IP	investigational products
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
LDAC	low dose cytarabine
MEC	mitoxantrone, etoposide and cytarabine
MM	multiple myeloma
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
N/A	not applicable
NCI CTCAE v4.03	National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

Term	Definition
OR	overall remission
OS	overall survival
PD	pharmacodynamics
PD	progressive disease
PK	pharmacokinetics
PR	partial remission
RBC	red blood cell
RO	receptor occupancy
SAE	serious adverse event
SC	subcutaneously
SOP	standard operating procedures
T-HALF	half life
Tmax	time of maximum observed concentration
TNF	tumor necrosis factor
Vss	apparent volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 1 2003 IWG RESPONSE CRITERIA FOR AML

Table 1: 2003 IWG Response Criteria for AML

Response	Definition	Criteria
CR	Morphologic leukemia-free state	Bone Marrow: < 5% blasts with normal maturation of cell lines. Peripheral blood: - Absolute neutrophil count > 1000/μL - Platelets ≥ 100,000/μL - Blasts 0% No residual evidence of extramedullary disease. Independent of RBC transfusions. No Auer rods present in bone marrow blasts.
CRi	Morphologic leukemia –free state with incomplete blood count recovery	Same criteria as CR except: platelet count < 100,000/μL and/or absolute neutrophil count < 1000/μL
PR	Regression of leukemia	≥ 50% decrease (from baseline) in the percentage of blasts to 5% to 25% in the bone marrow aspirate and all the hematologic values for CR. Bone marrow blasts <5% but with Auer rods present.
Treatment Failure (TF)	Failing to achieve a complete or partial remission	Failure to achieve a CR, CRi, or PR during the treatment period. Last posttreatment peripheral blood smear and/or bone marrow aspirate/biopsy show persistent leukemia.
Relapse (after CR/CRi)	Morphologic recurrence of leukemia	Reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributed to any other cause. Reappearance or development of cytologically proven extramedullary disease.
PD (after PR)	Morphologic increase in leukemia	50% increase (from nadir) in either leukemia peripheral blood involvement (absolute count), bone marrow leukemia infiltrate, or extramedullary site of disease, if applicable.

Abbreviations: CR = complete remission; CRi = complete remission with incomplete blood count recovery; PR = partial remission; PD = progressive disease; RBC = red blood cells.

Source: Cheson BD, Bennett JM, Kopecky KJ et al. Revised Recommendations of the International Working Group for diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003: 21: 4642-4649.

Leukemia responses will be assessed after each cycle as follows: CR, CRi, PR, TF, PD, or Relapse as described above. Local laboratory reports supporting assessments will be sent to BMS. Subjects without local laboratory reports will be recorded as not done.

APPENDIX 2 SIMULATION TO EXAMINE MTPI VS. TRADITIONAL 3+3 DESIGN FOR DOSE ESCALATION STUDY WITH 2 DOSE LEVELS

The dose escalation part of the study utilizes the mTPI method. The mTPI uses a set of decision rules guided by simple Bayesian models and requires a definition of an equivalence interval (EI), in which any dose is considered close to the true maximum tolerated dose (MTD). For this study, the EI is defined as [15%, 25%] with the target toxicity rate of 20%. With this method, there are 3 intervals in the toxicity probability scale: (0, 15%) that is considered lower than the target toxicity rate, [15, 25%] that is considered within the toxicity target range, and (25, 100%) that is considered toxic.

Using this mTPI design, initially 3 eligible subjects will be treated at the dose level of 600 mg. Any additional subjects will not be added to the same dose level, ie a total number of 3 subjects will be treated for a given dose level. A decision to stop the enrollment or to consider the next higher dose level (800 mg), will be guided by the number of subjects with dose-limiting toxicities (DLTs) observed (see Table 1).

Table 1: Guidance for Safety Monitoring Based on Observed DLTs

		Number of Subjects Treated at given dose level
		3
Number of Subjects with DLTs	0	E
	1	E
	2	DU
	3	DU

At Starting Dose (600 mg):
E: Escalate and enroll subjects to the next higher dose level
DU: The current dose is too toxic. Discuss of proceeding with the next lower dose level
At Maximum Dose (800 mg):
E: Current dose level is safe and stop enrollment
DU: The current dose is too toxic.

Simulations were conducted to examine the performances of the mTPI design and the traditional escalation 3+3 design for this study. The 3+3 design starts from the lower dose level (600 mg); adapts every cohort of 3 patients; considers the next dose level if unacceptable toxicity rate observed. The "1/3" rule has been used in the design, in the way below:

Initially, 3 subjects per level will be treated. If 0 out of 3 subjects experiences DLT, 3 subjects will be treated at the next higher dose level. If 1 out of 3 subjects experiences DLT, an additional 3 subjects at the same dose level will be treated. If 1 out of 6 subjects experiences DLT at a level, 3 subjects will be treated at the next higher dose level. If ≥ 2 out of 6 subjects, or ≥ 2 out of initial 3 subjects experience DLT at a dose level, then the MTD is considered to have been

exceeded, and 3 more subjects will be treated at the previous dose unless 6 subjects have already been treated at that dose. The MTD is defined as the highest dose at which not more than 1out of 6 subjects experience DLT.

The mTPI design is knowledge-driven, which assumes a target toxicity rate. On the contrary, the traditional 3+3 design is algorithm-driven, which uses the "1/3" rule.

Simulation Implementation:

- 10,000 simulated trials
- Target toxicity rate for the mTPI design: 20% with EI = [15, 25%]
- mTPI design and traditional 3+3 design as described above

Toxicity Scenarios for Each Dose Level:

Dose levels	1	2	3	4	5	6
600 mg	0.10	0.10	0.15	0.10	0.15	0.20
800 mg	0.15	0.20	0.20	0.25	0.25	0.25

Table 2: Simulation Results Summary

Scenario 1	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.1	0.15		
mTPI	3.0	5.9	91.1	12.4	5.9
Traditional 3+3	9.6	19.5	70.9	12.8	9.5
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (91% vs 71%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (9% vs 29%); the average toxicity rates for mTPI is slightly less than the traditional design; the average total number of subjects for mTPI is less than the traditional design.					
Scenario 2	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.1	0.2		
mTPI	3.0	10.2	86.9	14.9	5.9
Traditional 3+3	10.0	30.3	59.7	15.3	9.6
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (87% vs 60%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (13% vs 40%); the average toxicity rates for mTPI is slightly less than the traditional design; the average total number of subjects for mTPI is less than the traditional design.					

Scenario 3	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.15	0.2		
mTPI	6.1	9.8	84.1	17.4	5.9
Traditional 3+3	20.0	26.6	53.3	17.5	9.2
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (84% vs 53%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (16% vs 47%); the average toxicity rates for mTPI is slightly less than the traditional design; the average total number of subjects for mTPI is less than the traditional design.					
Scenario 4	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.1	0.25		
mTPI	2.2	15.3	82.5	17.4	5.9
Traditional 3+3	9.7	41.7	48.6	17.7	9.8
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (83% vs 49%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (18% vs 51%); the average toxicity rates for mTPI is slightly less than the traditional design; the average total number of subjects for mTPI is less than the traditional design.					
Scenario 5	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.15	0.25		
mTPI	5.8	14.8	79.4	19.8	5.8
Traditional 3+3	20.3	36.9	42.8	19.8	9.4
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (80% vs 43%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (21% vs 57%); the average toxicity rates for mTPI is the same as the traditional design; the average total number of subjects for mTPI is less than the traditional design.					
Scenario 6	% Selected			Average Toxicity rate	Average Total number of Subjects
	Under 600 mg	600 mg	800 mg		
		0.2	0.25		
mTPI	11.3	13.9	74.8	22.3	5.7
Traditional 3+3	31.9	30.2	37.9	22.3	8.7
Note: mTPI design selects the correct dose (800 mg) more frequently than the traditional designs (75% vs 38%); the Traditional design selects sub-optimal dose (600 mg and under 600 mg) more frequently (25% vs 62%); the average toxicity rates for mTPI is the same as the traditional design; the average total number of subjects for mTPI is less than the traditional design.					

In summary, the mTPI design selects the correct dose (800 mg) more frequently than the traditional 3+3 design for all the scenarios under the true toxicity rate within EI evaluated. The average toxicity rates for mTPI design are similar to the rates of the traditional designs and closer to the target toxicity rate of 20% in most cases. The average of total number of subjects for mTPI design is less than the traditional designs in all cases. The traditional 3+3 design is more conservative and may select sub-optimal dose frequently.

APPENDIX 3 WHO CLASSIFICATION OF AML

Table 1: WHO Classification of AML

Acute myeloid leukemia
Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
AML with mutated *NPM1*
Provisional entity: AML with BCR-ABL1
AML with biallelic mutations *CEBPA*
Provisional entity: AML with mutated RUNX1
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

Note: Subjects with APL will be excluded from this study.

Source(s): Swerdlow SH, Campo E, Harris NI et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Lyon: IARC press; 2008.

Arber DA, Orazi A, Hasserjian R et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016: 127: 2391-2405.

APPENDIX 4 ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Women must follow instructions for methods of contraception for the duration of treatment with study drugs, ulocuplumab and cytarabine (LDAC), plus 5 half-lives of the study drug (48 days) plus 30 days (duration of ovulatory cycle) for a total of 78 days post-treatment completion.

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

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

NOTES:

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

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

[c] These methods are not approved nor certified in Japan.

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

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female[c] condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide[c] • Cervical cap with spermicide[c] • Vaginal Sponge with spermicide[c] • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only [c] • Lactation amenorrhea method (LAM)

These methods are not approved nor certified in Japan.

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

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

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

Males who are sexually active with WOCBP must agree to follow instructions for methods of contraception for the duration of treatment with study drugs, ulocuplumab and cytarabine (LDAC), plus 5 half-lives of the study drug (48 days) plus 90 days (duration of sperm turnover) for a total of 138 days post-treatment completion.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.3 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 6 HEMATOPOIETIC CELL TRANSPLANTATION (HCT) – SPECIFIC COMORBIDITY INDEX

Comorbidity	Definition of Comorbidity	Score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease (one or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft); congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3