CCB-01

STUDY PROTOCOL

A Phase 1b/2a open-label, multi-center study to assess the safety, efficacy and pharmacokinetics of intrapatient dose-adjusted brequinar and inhibition of dihydroorotate dehydrogenase (DHODH) in adult subjects with acute myelogenous leukemia (AML)

NCT03760666

Statistical Analysis Plan – 09/11/2019

Novella CLINICAL
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Sponsor Approval Form

Project: YYA36071 Sponsor: Clear Creek Bio, Inc.
Date: 11 Sep 2019 Protocol: CCB-01

Item(s) Submitted for Approval	File name (for electronic documents)
☐ * System Configuration	
☐ * Rights and Roles	
☐ * eCRF Design – PDF of forms	
☐ * Edit Check Specifications	
☐ eCRF Completion Guidelines	
☐ SAE Reconciliation Guidelines	
☐ Coding Report	
☐ Randomization Schedule Specification	
☐ Randomization Plan	
☐ Unblinding Plan	
☐ Study Data Transfer Requirements	
☐ SDTM Specifications	
☐ SDTM Transfer	
☐ CDF Specifications	
☐ CDF Test Transfer	
☐ Site Payment Criteria Specifications	
☒ Statistical Analysis Plan – text	20190911 CCB-01 YYA36071 SAP v1.0.doc
☒ Statistical Analysis Plan – data display shells	20190911 CCB-01 YYA36071 TLF Shells.doc
☐ Statistical Reporting – TLF Delivery	
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- [None]

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11 September 2019
Date

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[Sponsor Title]; [Sponsor Company]

23 Sept 2019
Date

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Clear Creek Bio, Inc.

Protocol #: CCB-01

A Phase 1b/2a open-label, multi-center study to assess the safety, efficacy and pharmacokinetics of intrapatient dose-adjusted brequinar and inhibition of dihydroorotate dehydrogenase (DHODH) in adult subjects with acute myelogenous leukemia (AML)

Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Definition
ANC	Absolute neutrophil count
AE	Adverse event
AML	Acute myelogenous leukemia
$AUC_{0\text{-last}}$	Area under curve from time 0 to time of last measurable concentration.
$AUC_{0\text{-inf}}$	Area under curve from time 0 to infinity
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration
CR	Complete remission
CRh	CR with partial hematological recovery
Cri	CR with incomplete hematological recovery
C_{ss}	Observed concentration at steady state
CTCAE	Common terminology criteria for adverse events
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
FISH	Fluorescence in situ hybridization
Hgb	Hemoglobin
mg	Milligram
m^2	Meters squared
MedDRA	Medical dictionary for regulatory affairs
MLFS	Morphologic leukemia-free state
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PK	Pharmacokinetic(s)
PR	Partial remission
PT	Preferred term
SAP	Statistical analysis plan
SI units	International system of units
SOC	System organ class
$t_{1/2}$	Elimination half-life
T_{max}	Time to maximum plasma concentration
TEAE	Treatment-emergent adverse event
TI	Transfusion independence
TLF	Tables, listings, and figures

V_{ss}	Volume of distribution at steady state
WHODD	World health organization drug dictionary

I. Introduction

This Statistical Analysis Plan (SAP) presents details of the analyses required to address the study aims of protocol CCB-01 version 6.0, dated 30 April 2019. The study is a phase 1b/2a open-label, multi-center trial with a purpose to evaluate the safety, efficacy, and pharmacokinetics (PK) of the drug oral brequinar in subjects 18 years or older with relapsed/refractory acute myeloid leukemia (AML), as well as to determine the inhibitory level of brequinar in blocking the enzyme "dihydroorotate dehydrogenase" (DHODH).

Safety and tolerability of brequinar will be assessed via adverse event (AE) monitoring, clinical laboratory safety tests, physical examinations, vital signs measurements, 12-lead electrocardiogram (ECG) readings, and bone marrow sampling. Specific efficacy endpoints of disease response, and PK profiles of brequinar and dihydroorotate (DHO) plasma levels will also be characterized.

This SAP has been developed and approved prior to database lock and data analysis. All analyses will be conducted after clinical trial data are entered into the database, discrepancies resolved, and the database is authorized (closed to further changes). Any deviations from the SAP will be documented as such in the study report.

Production and quality control of statistical analyses and accompanying tables, listings, and figures (TLFs) will be the responsibility of IQVIA Biotech located in Morrisville, North Carolina, United States.

II. Protocol Objectives

A. Primary

The protocol lists the following primary objective:

- To determine the safety and tolerability of brequinar and the DHODH inhibitory activity of brequinar in adult subjects with AML.

B. Secondary

The protocol lists the following secondary objectives:

- To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR) (criteria as defined in the ELN Guidelines, by Dohner et al., 2017) and complete remission with partial hematological recovery (CRh).

- To assess the rate of overall survival (OS) and event-free survival (EFS).
- To evaluate duration of response (DOR).
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

C. Exploratory

The protocol lists the following exploratory objectives:

- To assess the relationship between DHODH inhibition and the efficacy and safety of brequinar.
- To evaluate molecular and cellular biomarkers that may be predictors of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment.
- To evaluate global gene expression profiles, deoxyribonucleic acid (DNA)methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.

III. Study Endpoints

A. Primary Endpoints

The study protocol defines primary endpoints as safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels.

Safety/tolerability, assessed at each study visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, will be evaluated for each subject as follows:

- Through Day 42, Grade 3 or higher, treatment-emergent, study drug-related, non-hematologic AE will be considered unacceptable toxicity with the following exceptions:

Condition	Exception Description
Nausea/ Emesis	Grade 3 nausea and/or emesis resolving to less than or equal to Grade 2 or baseline within 1 week after the use of an optimal antiemetic regimen based on standard practice.
Diarrhea	Grade 3 diarrhea resolving to less than or equal to Grade 1 or baseline within 1 week after receiving the maximal supportive therapy based on standard practice.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.
Mucositis	Grade 3 with duration < 1 week.
Fatigue	Grade 3 with duration < 2 weeks.

- After 42 days of treatment, criteria for unacceptable safety will be expanded to include hematologic AEs defined as:
  - Prolonged neutropenia with ANC < 500 from start of therapy in the absence of disease.
  - ≥ Grade 4 neutropenia.
  - And/or ≥ Grade 4 thrombocytopenia with a hypocellular bone marrow and no greater than 5% marrow blasts lasting for ≥ 2 weeks.

- After 42 days of treatment, in expansion cohort subjects, the definition of unacceptable safety will include signs of hepatotoxicity (an episode of ≥ Grade 2 toxicity for ALT and AST).

B. Secondary Endpoints

The following secondary endpoints will be analyzed:

- ORR including CR, CRi, CRh, MLFS, or PR.
- Rates of OS and EFS.
- Duration of response.
- PK profile of brequinar.
- DHO plasma profile.

C. Exploratory Endpoints

The following endpoints will be explored:

- Relationship between DHODH inhibition and the efficacy and safety of brequinar.
- Antitumor level based on molecular and cellular biomarkers including cytogenetics, molecular profiling, and flow cytometry during and after treatment.
- Global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.

IV. Study Design

A. Design Overview

This will be a phase 1b/2a multi-center, open-label, non-randomized clinical trial to assess the safety, tolerability and efficacy of dose-adjusted brequinar in adult subjects with AML. The study will also assess the inhibition of DHODH and the PK profile of brequinar in plasma. Intra-subject dosing will be adjusted based on safety/tolerability, brequinar PK, and DHO levels.

Up to 27 subjects are planned to be entered in this trial. Cohort 1 was planned to have 6 subjects, but enrollment was stopped after 5 subjects when brequinar PK and DHO results became available. These results led to study design changes as described here. The sixth subject will not be enrolled in Cohort 1.

Cohort 2 will enroll approximately 6 subjects, followed by an expansion cohort of approximately 15 subjects. All subjects in Cohort 2 will start with a 500 mg/m^2 dose once-weekly. Brequinar PK and DHO samples will be obtained for these subjects in Week 1 and results used to make decisions about the Week 2 once-weekly dose. Brequinar PK and DHO samples will also be obtained for Week 2 and the results used to make decisions about Week 3 dose frequency (once or twice-weekly) and the dose. The dose will be adjusted for each subject to meet the twice-weekly brequinar PK and 72-hour DHO criteria, and the Week 2 procedures may be repeated if needed until the twice-weekly dose is found.

After both the brequinar PK and 72-hour DHO level meet criteria described in the Individual Dose Adjustment Guidelines as described in Protocol Section 8.5, a subject may move to twice-weekly dosing on a continuing basis as tolerated. The twice-weekly dose may be further adjusted using 84-hour DHO (trough ~ 84 hours after dosing) criteria, also described in the Guidelines for Individual Dose Adjustment.

Dosing will continue up to 12 months in the absence of unacceptable toxicity or disease progression, or may be discontinued with Sponsor consent after completing at least 6 weeks of dosing.

B. Study Population

Up to 27 subjects 18 years or older with relapsed/refractory AML by World Health Organization (WHO) classification who have exhausted available therapy and who meet all inclusion/exclusion criteria will be enrolled at 3- 6 sites in the United States.

C. Sample Size Predictions

Formal sample size calculations are not applicable to this phase 1b/2a dose-adjustment and expansion study.

V. General Analytical Considerations

All analyses of safety and anti-leukemic activity for this open-label, early-phase study will be descriptive in nature and presented by dose group and overall, as appropriate, for dose-adjustment and expansion phases.

Statistical code and outputs for analyses will be generated using SAS/STAT and SAS/GRAPH software, version 9.3 or higher, of the SAS system for Windows. Copyright © [2011] SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

A. Data Sources

The study center staff will record completion and results of required study procedures in an electronic case report form (eCRF). The following external data obtained from third-party vendors for this study will be combined with eCRF data for analysis:

Vendor Name	Contact Information	Data Type	Schedule	Reconciliation Items
Pyxant	TBD	DHO plasma levels and brequinar PK results	2 transfers during study	Header data (subject ID, initials, visit, lab date, lab time)

B. Multiple Study Centers

Data analyses will be pooled and not controlled for center effect.

C. Definition of Baseline

Baseline will be defined as the last measurement collected before the first dose of study drug. As such, height and body surface area assessed at Screening, and pre-dose assessments made on Cycle 1 Week 1 Day 1 for weight, vital signs, hematology/chemistry, and 12-lead ECG will serve as valid baseline measures. A missing value at Cycle 1 Week 1 Day 1 will default to the Screening measurement.

For this study, since there is no day 0, the day immediately prior to study day 1 will be Day -1 [calculated as Event Date – Date of First Treatment]. For events on or after first dose of study drug, study day will be calculated as [Event Date – Date of First Treatment + 1]. Thus, first day of study drug dose will be Day 1.

D. Missing Data

Unless stated otherwise in sections below, missing data will not be replaced with imputed values.

E. Analysis Populations

Four analysis population sets will be defined for use with various analyses, namely:

- The Enrolled Analysis Set will include all subjects who sign informed consent, meet the inclusion/exclusion criteria and are enrolled in the study. Demographics and disposition summaries will be reported for this set of subjects.

- The Safety Analysis Set will include all subjects who are enrolled in the study and receive at least one dose of brequinar. Subjects in this set will be used for all safety/tolerability summary tables.

- The Efficacy Analysis Set will be a subset of the Safety population with measurable AML disease at baseline and at least one post-baseline disease response assessment. Subjects in this set will be used for all efficacy summary tables.

- Pharmacokinetic Analysis Set will be a subset of the Safety population with at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK. Summary tables for PK concentrations and parameters will be based on this set of subjects.

F. Data Display Characteristics

Data displays produced for this study will include three types—data listings, summary tables, and figures.

Unless stated otherwise, data listings will be produced for all recorded data. Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, subject number, and date and time of assessment, where applicable. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Additional listings may be produced for outcome measures that involve extensive procedure to derive analyzed outcomes.

Summary tables will display summary statistics calculated for each of the treatment groups, and overall. When the evolution of statistics over time is of interest, a group of rows that represent a cohort would generally be ordered chronologically.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Continuous data will be summarized with the number of nonmissing values, mean, standard deviation (SD), minimum, median, and maximum. Categorical data will be summarized with the number of nonmissing values. Corresponding percentages will be calculated using the relevant analysis population set as the denominator, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

PK concentrations and parameters will be summarized using n (for available data), mean, SD, coefficient of variation percent (CV%), median, minimum, and maximum values. Geometric means and geometric CV% will also be calculated for PK parameters.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry.

Extra measurements (such as unscheduled or repeat assessments) will be included in subject listings but not in summary tables.

Figures will be produced as specified in sections to follow.

VI. Subject Accountability

A. Analysis Populations

A summary table will present counts and percent of subjects in the study analysis populations of Enrolled, Safety, Efficacy, and PK Analysis sets by treatment group.

B. Disposition

All subjects who discontinue treatment or withdraw early from the study will be included in a listing. Disposition summaries will present number of subjects enrolled, number treated, and among those treated number who completed and discontinued treatment. Primary reason for discontinuation of treatment, including any of the following, will be summarized:

- Adverse event
- Physician/Sponsor decision
- Pregnancy
- Protocol defined disease progression
- Study terminated by sponsor
- Subject non-compliance/Protocol violation(s)
- Withdrawal of consent.

Counts and percentages of subjects who withdraw early from the study for any of the above reasons will also be calculated using all members of the relevant population in the relevant treatment group for the denominator.

C. Subject Characteristics

The following subject characteristics collected for the Enrolled Analysis Set will be presented in data listings and summarized by treatment regimen and overall:

Demography:

- Age: Age will be calculated as the number of years elapsed between birth date and the date of the screening visit, adjusted for whether the birthday has passed as of the day of the screening visit.
- Sex at birth
- Ethnicity
- Race

Medical History:

- Medical history: As noted on the Medical History eCRF, any significant medical conditions present prior to signing consent will be presented in a listing and summary table. Verbatim terms will be coded using the MedDRA version 21.1 and ordered by system organ class (SOC) and preferred term (PT). At each level of summation (SOC, PT), subjects reporting more than one medical condition will be counted only once.
- AML disease information: Disease characteristics of initial diagnosis of AML recorded on the eCRF, along with time since initial diagnosis (calculated as date of informed consent – date of initial diagnosis of AML/365.25), will be listed and summarized.
- AML supplemental tests: Cytogenetics and molecular data information recorded on the eCRF will be listed, including information on karyotypic, Fluorescence in situ hybridization (FISH), and gene fusion analysis, as well as all present mutations.
- Prior cancer drug treatment: A listing will display all entries for prior cancer medications received by a subject, ordered by "Start date". A summary table will summarize the following characteristics:
    - Number of subjects reporting at least one prior cancer drug treatment.
    - Drug treatment type (Chemotherapy, Targeted therapy, Immunological, Not Applicable) .
    - Drug treatment combined with radiotherapy (No/Yes).
    - Number of cycles received.
    - Best response under treatment (Complete remission, Complete remission with incomplete hematologic recovery, Complete remission with partial hematologic recovery, Morphologic

leukemia-free state, Partial remission, Stable disease, Progressive disease, Unknown).

- Relapse (derived as 'Yes' if date of relapse is not blank. 'No' otherwise).

- Prior cancer non-drug treatment: All non-drug treatments received will be listed in order of "Start date". Summary statistics will be provided for:
  - Number of subjects reporting at least one prior cancer non-drug treatment.
  - Treatment type (Radiation, Surgery, Other).
  - Intention (Palliative, Therapeutic).
  - Best response under treatment (Complete remission, Complete remission with incomplete hematologic recovery, Complete remission with partial hematologic recovery, Morphologic leukemia-free state, Partial remission, Stable disease, Progressive disease, Not applicable, Unknown).
  - Relapse (derived as 'Yes' if date of relapse is not blank. 'No' otherwise).

D. Protocol Deviations

A listing will be provided for all protocol deviations.

VII. Safety Analyses

To meet the primary objective of the study, all safety analyses will be performed on the Safety Analysis Set of subjects.

A. Exposure

For each subject, the assigned dose level of brequinar (mg/m^2), the assigned dose (mg), dose day, date and time taken, whether entire dose was taken, number of capsules taken, total dose taken (mg), and the reason for missed dose (partial or complete) will be listed by treatment group and visit cycle.

Summary statistics will be presented for assigned dose level, cumulative assigned dose, cumulative actual exposure (mg), total duration of treatment (calculated as the number of weeks from date of first drug dose to date of last drug dose), dose intensity (calculated as cumulative actual exposure divided by treatment duration, mg/week), relative dose intensity (calculated as a percent of cumulative actual drug dose divided by cumulative assigned dose), and any reason for missed dose.

B. DHO Plasma Levels

In addition to safety/tolerability, intra-subject dosing for this study will be guided by DHO levels measured using a validated assay. A subject listing will include baseline and trough DHO levels (ng/ml), as well as the following additional characteristics noted at each scheduled visit:

- Previous assigned dose (mg/m^2).
- DHO dose adjustment (dose not changed, escalated by 150 mg/m^2, held, Cohort 1 dose escalation not permitted).
- Assigned dose based on DHO (mg/m^2).
- PI evaluation of whether subject has acceptable safety, safety dose adjustment, and assigned dose.
- Actual dose (mg).
- Agreement between PI assessment and actual dose (No/Yes, reason for disagreement).

The above dose-modification characteristics will also be summarized by treatment group and overall.

C. Dose Limiting Toxicities

AEs identified as protocol-defined DLTs will be listed and will include start and end dates, CTCAE grade, relationship to study drug, outcome, and action taken. Number and percentage of subjects reporting DLTs in each treatment group, and overall, will be summarized.

D. Adverse Events

AEs will be collected from time of informed consent through at least 14 days after the final dose of study medication. Any pre-existing condition that changes in severity after dosing or abnormal laboratory finding will be recorded as an AE. Events that occur prior to dosing will be recorded as medical history. A TEAE for this study will be defined as an AE occurring after the first dose of the study treatment through 30 days after the last dose of study treatment.

Verbatim terms on the eCRF will be coded using the MedDRA version 21.1 and displayed hierarchically by system organ class and preferred term. Multiple incidences of the same AE for a subject will be counted only once at the maximum CTCAE grade.

All AEs (whether TEAEs or not) will be listed by treatment group and individual subject, and include start and end dates, if the event was serious, seriousness criteria, CTCAE grade, relationship to study drug, action taken with study drug, and any other action. All TEAEs, Serious TEAEs, TEAEs that lead to study drug being permanently discontinued, and TEAEs resulting in death will be listed separately.

All AEs (whether TEAEs or not) will be summarized by system organ class and preferred term for each treatment group.

An overall summary table for TEAEs, and TEAEs occurring 10% or higher in the study population by preferred term and CTCAE grade will be provided. All TEAEs, grade 3 or greater TEAEs, TEAEs related to study drug (i.e., relationship to study drug deemed by the principal investigator as “Definite”, “Probable”, or “Possible”), grade 3 or greater TEAEs related to study drug, serious TEAEs, TEAEs leading to study drug being permanently discontinued, and TEAEs resulting in death will each be summarized by system organ class and preferred term. At each level of summation of system organ class and preferred term, subjects reporting more than one AE will only be counted once.

E. Deaths

All deaths and the primary cause of death will be listed.

F. Clinical Laboratory Results

Clinical laboratory tests for safety will be performed according to the study schedule, samples analyzed at local laboratories, and data entered directly into the electronic data capture system by site users.

Results for hematology and chemistry panels will be presented in separate data listings along with a flag for normal, abnormal not clinically significant, or abnormal clinically significant values. Listings will also be provided for pregnancy test, flow cytometry, and chromosomal/mutation testing.

Beginning with the baseline results, summaries of actual values at each assessment time point, and change from baseline will be presented by dose level and overall for each hematology and chemistry parameter. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

For hematology parameters leukocytes, hemoglobin, and platelets that can be graded using the NCI CTCAE criteria, shift tables that summarize counts and percentages of subjects by severity grade at baseline and worst post-baseline result will also be constructed.

The percentage of blasts in bone marrow ascertained via aspiration and biopsy will be listed and summarized.

G. Vital Signs

At designated visits, vital signs will be recorded and will include weight, temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure. A listing of all vital signs, along with height and derived body surface area, will be provided. Additionally, data will be summarized by dose group and overall, using descriptive statistics at baseline, each study evaluation, and change from baseline to evaluation. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either value is missing, the observation will not be included in the change from baseline summary.

H. 12-Lead Electrocardiogram

12-lead ECG data, obtained at scheduled visits, will be listed. Counts and percentages of subjects with normal, abnormal clinically significant, and abnormal not clinically significant evaluations will be summarized at each time point.

I. ECOG Performance Status

ECOG performance status assessed at Screening will be listed and summarized for each numeric grade.

J. Physical Examination

Confirmation of a physical examination, including date of assessment, will be listed for each scheduled time point.

K. Concomitant Medications

Any medication or treatment taken within two weeks prior to study entry as well as during the course of the study will be recorded in the eCRF. Indication for use, start date (if known), dose frequency, route, and whether ongoing or stopped will also be noted.

Verbatim terms from the eCRF will be mapped to Anatomical/Therapeutic Chemical class and Generic drug names using the WHODD version September 2018 Enhanced B2.

For each dose cohort, a listing will display all entries for medications received by a subject, ordered by “Start date”. The listing will display the recorded term from the eCRF and, adjacent to that, the WHO Drug pharmacological subgroup and the anatomical main class that appears in the tables.

A summary table will be constructed to display the anatomical main class (1st level) of each coded medication and, within that, the pharmacological subgroup (3rd level). It will include counts and percentages of subjects who reported using at least one medication in each pharmacological subgroup.

L. Blood Transfusions

Any blood transfusions received up to eight weeks prior to Cycle 1 Day 1 (baseline event), and during the study, including start and end dates, blood product, total number of units received, and reason for transfusion will be listed and summarized.

VIII. Efficacy Analyses

The secondary objectives of the study will be addressed using the Efficacy Analysis Set of subjects.

A. Disease Response

As per criteria defined in the ELN Guidelines by Dohner et al, 2017, disease response will be assessed at screening and post-screening visits and included in a data listing. Additionally, anti-leukemic activity will be evaluated as per the following outcomes:

Response Rates: The distribution of best overall response (BOR) of CR, CRi, CRh, MLFS, or PR will be summarized by treatment cohort and overall. Point estimates with two-sided exact 95% and 90% confidence intervals (CIs) will be included for:

- Overall response rate (ORR) defined as the proportion of subjects who achieve a best overall response of CR, CRi, CRh, MLFS, or PR.
- Complete remission rate defined as the proportion of subjects who achieve a best overall response of CR.
- Complete remission with incomplete hematologic recovery rate defined as the proportion of subjects who achieve a best overall response of CRi.
- Complete remission with partial hematological recovery rate defined as the proportion subjects who achieve a best overall response of CRh.
- Morphological leukemia-free state rate defined as the proportion of subjects who achieve a best overall response of MLFS.
- Partial remission rate defined as the proportion of subjects who achieve best overall response of PR.

Additional information on precise definitions of these response categories can be found in Section 10.3 of the protocol.

Duration of Response: Duration of response will be defined as the time from the first occurrence of a qualifying response of CR, CRi, CRh, MLFS, or PR, to the date when progressive disease is objectively documented or death due to any cause, whichever occurs earlier. Following the qualifying response, subjects who are alive without disease progression will be right-censored at the date of last disease evaluation. A Kaplan-Meier graph will be plotted by treatment group and estimates of median duration with associated 95% CIs will be reported.

Event-free Survival (EFS): Event-free survival will be determined from the first dose of brequinar to the date of relapse ($\geq$ 5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death, whichever occurs first. Subjects who do not experience any of the three events will be right-censored at the latter date of disease evaluation or bone marrow sampling. A Kaplan-Meier graph will be plotted for time to the composite outcome by treatment group, and the estimate of medial survival time with 95% CI will be summarized.

Overall Survival (OS): Overall survival will be calculated as the time from the first dose of study drug to the date of death or right-censoring at the date of last subject contact. Median time to OS, with 95% CI, will be summarized and displayed graphically by treatment group using the Kaplan-Meier method.

B. Clinical Benefit

In addition to ORR, this study will examine clinical benefit to subjects. By treatment group, a summary table will report counts and percent of transfusion-dependent subjects at baseline who, in the absence of progression, CR or PR, and independent of marrow response, achieve one of the following:

- Erythroid response: Transfusion Independence (TI) for 8 or more weeks for subjects requiring at least 4 units of packed red blood cell transfusions in the previous 8 weeks. Only red blood cell transfusions given based on physician's judgment for a pretreatment hemoglobin (Hgb) of $\leq$ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response: TI for subjects requiring a minimum of 4 platelet transfusions in the previous 8 weeks.

IX. Pharmacokinetic Analyses

The plasma PK of brequinar and DHO will be characterized using non-compartmental analysis. Where possible, the following standard PK parameters will be calculated:

- $AUC_{0\text{-last}}$: Area under plasma concentration-time curve from time 0 to time of last measurable concentration.

- $AUC_{0\text{-}inf}$: Area under plasma concentration-time curve from 0 to infinity.
- C_{max}: Maximum observed plasma concentration.
- C_{ss}: Observed plasma concentration at steady-state.
- CL: Systemic clearance.
- T_{max}: Time to maximum plasma concentration.
- $T_{1/2}$: Elimination half-life
- V_{ss}: Volume of distribution at steady state.

Listings of PK concentration and parameters will be generated using the Pharmacokinetic Analysis Set of subjects. Concentration and PK parameters will also be tabulated and summarized by treatment group at baseline and scheduled time points using descriptive statistics.

A listing of derived time interval between Brequinar dosing and pre-dose PK sampling will be provided.

Mean concentration-time profiles by treatment group, as well as by-subject plots for observed concentrations of brequinar and DHO levels will be presented on linear and semi-logarithmic scales.

Relationship between PK parameters, DHO levels, and clinical outcomes (e.g. efficacy, toxicity) may be explored.

X. Exploratory Analyses

This study will endeavor to explore the following aims:

Relationship between DHODH inhibition and the efficacy and safety of brequinar:

Identify molecular and cellular biomarkers predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling and flow cytometry during and after treatment:

Evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers as predictors of antitumor activity and/or resistance to treatment.

XI. Changes from Analyses Planned in Protocol

There are no significant changes to the analyses planned in the study protocol.

XII. References

1. CCB-01 Protocol_ver_5_16OCT2018-FINAL.pdf

2. CCB-01 Protocol_ver6_30APR2019 FINAL_signed 15MAY2019.pdf

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