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)

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CCB-01 Approvals and Revision History

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1.0	31 May 2018
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STUDY PROTOCOL

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Study No: CCB-01

Version Date: 4 June 2018

Sponsor:

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal Dose$_{(10\%, 50\%, 90\%)}$
LPS	Lipopolysaccharide
M	Molar
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar

Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	● To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. ● To characterize the pharmacokinetic (PK) profile of brequinar. ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. ● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.

Design	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. Subject dosing will be adjusted based on safety/tolerability and DHO level. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each may be added if the Cohort 1 starting doses require adjustment. Following completion of enrollment in the cohort dose-adjustment part of the study, an expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 – 3. Safety and tolerability will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling, and adverse event reporting. Bone marrow sampling (bone marrow aspirate and core biopsy) will also be utilized for efficacy. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	● Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	● Rates of treatment-emergent adverse events. ● Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. ● Event free survival (EFS). ● Duration of response. ● PK profile of brequinar. ● DHO plasma profile.
Exploratory endpoints:	● 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
Sample Size:	Up to 27 subjects

Number of Sites:	3 – 5
Study Period:	An enrollment period of 18 - 24 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial. 2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission. 3. ECOG Performance Status 0 to 2. 4. Cardiac ejection fraction ≥ 40% 5. Adequate hepatic function (unless deemed to be related to underlying leukemia). a. Direct bilirubin ≤ 2 x ULN b. ALT ≤ 3 x ULN c. AST ≤ 3 x ULN 6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation. 7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease. 8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration. 9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

Exclusion Criteria:	1. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to meet this criterion). 2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 4. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. b. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome. 5. AML relapse less than 6 months following stem cell transplantation. 6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 7. Active cerebrospinal involvement of AML. 8. Diagnosis of acute promyelocytic leukemia (APL) 9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 11. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy.

	12. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.
Treatment	Subjects will self-administer oral brequinar twice weekly (every 84 hours +/- 6 hours). Treatment cycles will be 2 weeks. Visits will take place at least every 2 weeks through 3 months; visits thereafter will be every 2 – 4 weeks at the discretion of the investigator at each site. Inter-cohort and intra-subject dose adjustments may occur throughout the study as outlined in the sections below.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: - Demographics (height, weight, date of birth, gender, race, ethnicity) - Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) - Concomitant medications. - Physical examination (including weight). - Vital signs (heart rate, respiratory rate, blood pressure, body temperature). - Pregnancy test for women of childbearing potential (WOCBP). - ECOG performance assessment. - Hematology/chemistry. - 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function. - Bone marrow sampling - Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. **Cycle 1 Day 1:** - Collect any adverse events or new concomitant medications since Screening. - Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. - Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP, and 12-lead ECG. - Review results and confirm subject remains eligible for the study.

	– Determine subject's starting dose based on the respective cohort mg/m^2 starting dose. – Dispense study medication. – Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. – Enroll subject for text message reminders if the subject consents to that service. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 2**: – Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 3**: – Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 4**: – Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. **Cycle 1 Day 8**: – Vital signs. – Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication.

	– Process and store brequinar/DHO samples per the supplied laboratory manual. – Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8). **<u>Cycle 2 (and any Dose Adjustment Cycle)</u>** Repeat this visit as needed whenever any dose adjustment is required. **Day 1:** – Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. – Take vital signs and perform physical examination (including weight). – Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below. – If dosing will continue, dispense study medication. – Dispense calendar/diary. – Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) **Day 8:** – Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. – Vital signs. – Collect pre-dose brequinar/DHO and hematology/chemistry samples. – Perform bone marrow sampling for flow cytometry (window ±7 days). – If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose. – Process and store brequinar/DHO samples per the supplied laboratory manual. – If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose.

	– Continue to withhold study drug if safety remains unacceptable. – Dispense calendar/diary. – Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) – Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8). Subjects may undergo dose adjustments at any time using the guidelines presented above. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects. Dose adjustments are permitted throughout the study for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. **<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)** Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle. In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow aspiration as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks (visit interval at the investigator's discretion). A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response (Figure 1). **Day 1:** – Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. – Collect pre-dose brequinar/DHO and hematology/chemistry samples. – Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (note that bone marrow is collected on study Day 22 (C2D8 ± 7 days), at Day 43, and then every 12 weeks; only the Day 43 sample will be assessed for hematological toxicity).

	– Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety). – Dispense study medication. – Dispense calendar/diary. – Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) – Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples. **Final Visit** This visit is to take place when a subject is discontinuing from the study. – Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. – Collect brequinar/DHO and hematology/chemistry samples. – Collect unused study medication. – Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (do not collect bone marrow if < 4 weeks since previous bone marrow sample obtained). – Review the safety information and determine whether the subject has acceptable safety or unacceptable safety. – Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples. – Stop text message reminders. **Follow Up Visit (2 weeks after Final Visit)** – Contact subject to elicit information about AEs/new concomitant medications since the last visit. Survival information will be collected while the study is ongoing. **Unscheduled Visits** Unscheduled visits and tests to assess AEs are permitted as needed.
Safety/ Tolerability	**Safety/Tolerability – Subject Level** Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.

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Exceptions to Grade 3 Nonhematologic AEs

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.
Fatigue	Grade 3 fatigue lasting less than 1 week.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.

Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as ≥ Grade 4 neutropenia and/or thrombocytopenia, with a hypocellular bone marrow and no greater than 5% marrow blasts lasting for ≥ 2 weeks. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

Safety/Tolerability – Cohort Level

Acceptable safety for a cohort starting dose is defined as having acceptable safety for the majority of subjects in that cohort at that starting dose (e.g., 4 out of a cohort's 6 subjects have no non-hematologic AEs ≥ Grade 3 with exceptions noted in table above).

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<tr><td>Cohort Starting Doses</td><td>

Cohort 1 will treat 6 subjects at a starting dose of 500 mg/m^2 twice weekly.

If there is unacceptable safety/tolerability and/or inadequate DHO level at a starting dose for the majority of subjects in a cohort, up to two additional cohort(s) of 3 subjects will be added. The starting doses for each subsequent cohort may be increased or decreased by up to 300 mg/m^2 up to a maximum starting dose of 800 mg/m^2 based on both safety/tolerability and adequacy of DHO level. Cohort starting doses will be jointly determined by the Sponsor and investigators and communicated to the study teams.

See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.

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<tr><td>Expansion Cohort</td><td>

Once a cohort starting dose has been reached that has adequate DHO level and acceptable safety/tolerability in a majority of the cohort's subjects, 15 subjects will be added at that cohort's starting dose. Decisions about

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<tr><td></td><td>adequacy of DHO level will be made following review of these data from each cohort. These subjects may also undergo individual dose adjustment.</td></tr>
<tr><td>Individual Dose Adjustment Guidelines</td><td>Intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments within the first 42 days of initiating treatment. Each subject's dose can be escalated, maintained (stable dose), held then reduced, or discontinued. The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned.

As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO level (Figure 1). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels and bone marrow results have been reviewed.

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at the higher of either 100 ng/mL or 2X the subject's baseline DHO level (see the brequinar Investigator's Brochure (IB)). This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

The intrasubject dose-adjustment criteria are presented below.

Intrasubject Dose Adjustment Criteria
<table>
<tr><th>Acceptable Safety/Tolerability? (see safety definition above)</th><th>Adequate DHO Level?</th><th>Planned Intra-Subject Dose Adjustment</th></tr>
<tr><td>Yes</td><td>Yes</td><td>Maintain; continue at same dose.</td></tr>
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<tr><td></td><td>
<table>
<tr><td>Yes</td><td>No</td><td>Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.</td></tr>
<tr><td>No</td><td>Regardless of DHO</td><td>Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week.
If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.</td></tr>
</table>
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<tr><td>Brequinar/DHO</td><td>Plasma brequinar/DHO samples are to be obtained for each subject for the first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to subjects in the expansion cohort who will have trough sampling only prior to the start of each two-week cycle.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour post dose brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.</td></tr>
<tr><td>Statistical Analysis</td><td>A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided.</td></tr>
</table>

	All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first

	dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

STUDY PERSONNEL

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STATISTICAL ANALYSIS

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2 INTRODUCTION

2.1 Background: Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10%.[1] It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

2.2 Dihydroorotate dehydrogenase (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous enzyme, and lack of its level is not compatible with life. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng 2010). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang 2002). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

2.3 Brequinar

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity

against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar was evaluated decades ago in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989, Burris 1998, Noe 1990, Schwartsmann 1990). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

2.4 Rationale for the Planned Trial

This study is designed to obtain safety and efficacy data for brequinar in patients with AML.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in more detail in Section 7.5.

2.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek proposes to use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional

rest period as is generally required between infrequent high doses. There will instead be twice-a-week administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the brequinar IB), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a biweekly schedule of brequinar dosed approximately every 84 hours, while measuring plasma DHO to fine-tune the dosing schedule that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggest that a starting dose for Cohort 1 of 500 mg/m^2 p.o. will be safe and well-tolerated in subjects with AML. Each subject's subsequent dosing may be adjusted depending on the safety, tolerability and DHO level obtained during the period following dose adjustment. Each of the two planned subsequent cohorts may also have an adjusted starting dose, again depending on safety, tolerability and DHO level observed in previous cohorts. See Section 7.4.

2.5 Risk/Benefit of Brequinar

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of AML is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment in patients with AML is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with AML typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

2.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the

guidelines presented in Section 9.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and treatment are described in Sections 9.10 and 9.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 9.7.

2.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

2.7.1 CYP Interactions

No formal drug-drug interaction studies have been performed with medications commonly used in treating AML. The nonclinical studies have demonstrated there is no first-pass metabolism, and there have been no apparent hepatotoxic effects in the clinical studies performed to date.

2.8 Steps to be Taken to Control or Mitigate Risks

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 9.

3 TRIAL OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML.

3.2 Secondary Objectives

The secondary objectives of this study are:

- 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 Döhner 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

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

4 TRIAL DESIGN

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 may be adjusted based on safety/tolerability and DHO level.

Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting dose. Following completion of enrollment in the cohort dose-adjustment part of the study, an expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized for efficacy. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in more detail in Section 7.

5 TRIAL ENDPOINTS

5.1 Primary Endpoint

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

5.2 Secondary Endpoints

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

5.3 Exploratory Endpoints

- 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

6 TRIAL POPULATION

6.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

6.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial.
2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.
3. ECOG Performance Status 0 to 2.
4. Cardiac ejection fraction ≥ 40%
5. Adequate hepatic function (unless deemed to be related to underlying leukemia)
    a. Direct bilirubin ≤ 2 x ULN
    b. ALT ≤ 3 x ULN
    c. AST ≤ 3 x ULN
6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation
7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

6.3 Exclusion Criteria

1. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to meet this criterion).
2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.

3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.
4. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:
    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.
    b. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.
5. AML relapse less than 6 months following stem cell transplantation.
6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).
7. Active cerebrospinal involvement of AML.
8. Diagnosis of acute promyelocytic leukemia (APL).
9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.
10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.
11. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
12. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

6.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

7 STUDY TREATMENTS

Subjects will self-administer oral brequinar twice weekly (approximately every 84 hours). Treatment cycles will be 2 weeks. Dose adjustment is to occur as outlined below. Visits will take place at least every 2 weeks through 3 months. More frequent visits are permitted to assess and/or treat adverse events. Less frequent visits (up to 4-week intervals) are permitted after 3 months depending on subject safety/tolerability and response. Inter-cohort and intra-subject dose adjustments are permitted depending on safety and plasma DHO levels. Cohort 1 will begin at 500 mg/m^2 twice weekly and will follow the cohort dose-adjustment scheme shown below. Subsequent cohorts will have a starting dose that has been adjusted based on the safety/tolerability and DHO levels of the previous cohort. The dosing for individual subjects may be adjusted based on the safety/tolerability and DHO levels as shown in Section 7.5.

7.1 Description of Brequinar:

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis based on the starting dose of a subject's cohort and the tolerability, safety and DHO level assessed following each dose. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 8 hours after the missed dose. If more than 8 hours have elapsed or if the dose was vomited or if the subject for any reason is unable to take the scheduled dose within 8 hours, omit that dose, and the subject should resume treatment with the next scheduled dose. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

7.2 Treatment Administration

Subjects will take oral brequinar twice weekly (approximately every 3.5 days) e.g., Monday morning and Thursday evening. Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar brequinar/DHO samples. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

7.3 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Safety/tolerability will be used to determine both individual cohort starting doses and dosing adjustments. Safety at the subject level is defined in Section 7.3.1; hematologic toxicity is defined in Section 7.3.1.1; and safety at the cohort level is defined in Section 7.3.1.1.

7.3.1 Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting

during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in Table 1.

Table 1. Exceptions to Grade 3 Nonhematologic AEs

Condition	Exception Description
Nausea/ Emesis	Grade 3 nausea and/or emesis resolving 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 ≤ Grade 1 or baseline within 1 week after receiving the maximal supportive therapy based on standard practice.
Fatigue	Grade 3 fatigue lasting less than 1 week.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.

7.3.1.1 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as ≥ Grade 4 neutropenia and/or thrombocytopenia, with a hypocellular bone marrow and no greater than 5% marrow blasts lasting for 2 weeks or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

7.3.2 Safety/Tolerability – Cohort Level

Acceptable safety for a cohort starting dose is defined as having acceptable safety (see Section 7.3.1) for the majority of subjects in that cohort at that starting dose (e.g., 4 out of a cohort's 6 subjects have no non-hematologic AEs ≥ Grade 3 with exceptions noted in Table 1).

7.4 Cohort Starting Doses

Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly.

If there is unacceptable safety/tolerability and/or inadequate DHO level at a starting dose in the majority of subjects in a cohort (see Section 7.3.1), up to two additional cohort(s) of 3 subjects will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level. The starting doses for each subsequent cohort may be adjusted by up to 300 mg/m^2 based on both safety/tolerability and adequacy of DHO level. Cohort starting doses will be determined by the Sponsor and communicated to the study teams. The planned upper limit for cohort starting dose is 800 mg/m^2.

7.5 Individual Dose Adjustment Guidelines

Intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments within the first 42 days of initiating treatment. Each subject's dose can be escalated, maintained (stable dose), held then reduced, or discontinued. The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned.

As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO levels. Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels and bone marrow results have been reviewed.

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at the higher of either 100 ng/mL or 2X the subject's baseline DHO level. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

Table 2 and Figure 1 present the intra-subject dose-adjustment criteria.

Table 2. Intra-Subject Dose Adjustment

Acceptable Safety/Tolerability? (see safety definition above)	Adequate DHO Level?	Planned Intra-Subject Dose Adjustment
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days

		after last dose of study drug or until AEs have resolved or become stable.

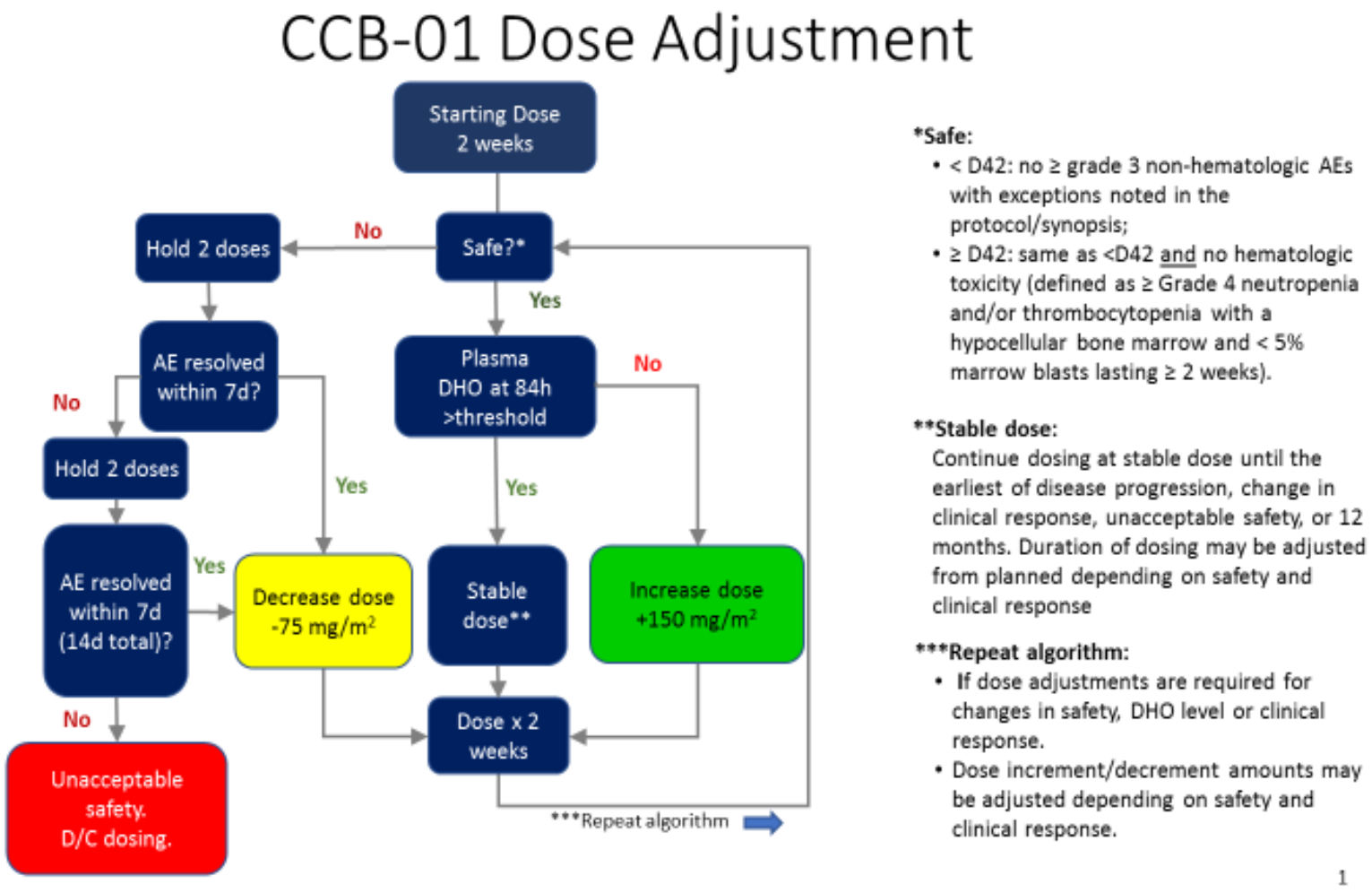

Figure 1. Dose Adjustment – Subject Level

7.6 Medication/AE Diary

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

7.7 Bone Marrow Biopsy

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the C2D8 visit ± 7 days, and one at Day 43 ± 7 days; thereafter, bone marrow sampling will be done every 12 weeks and at the Final Visit. If a participant develops frank evidence of progression of AML during the course of treatment based on laboratory or clinical assessment, then he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at the Day 43 visit, then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for the Day 43 visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

7.8 Flow Cytometry

Peripheral blood samples are to be obtained for flow cytometry in Cycle 1 at baseline (Day 1 pre-dose), Day 2, and Day 3.

7.9 Expansion Cohort

Once a cohort starting dose has been reached that has adequate DHO level (as mentioned above, “adequate” trough DHO may be adjusted after reviewing DHO level, safety and clinical response data) and acceptable safety/tolerability in a majority of the cohort’s subjects, 15 subjects will be added at that cohort’s starting dose. Subjects in this cohort are eligible for intra-subject dose adjustment (see below).

7.10 Study Drug Discontinuation

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh), the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued if there is evidence of unacceptable safety/tolerability that does not resolve within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 30 days after the last dose of brequinar or until they receive another treatment for their AML. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

7.11 Brequinar Pharmacokinetics (PK) / Dihydroorotate (DHO) Plasma Levels

Plasma samples for brequinar/DHO levels are to be obtained for each subject for the subject's first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is baseline at 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to Cycle 1 for subjects in the expansion cohort, see below.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84h}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.

Directions regarding sample processing are presented in a separate laboratory manual.

7.12 Concomitant Medication/Treatment

The name, start date (if known), indication for use and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;
- Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.

7.12.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

7.13 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

7.14 Storage, Stability, Labeling and Packaging

7.14.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

7.14.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-01

Contents: 100 or 250 mg capsules

For oral use only. Take with approximately 8 ounces water every 3.5 days.

Subject Number: XX-XXXX

Treatment Duration: As directed

IND: 138355 Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

7.14.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution. No randomization codes are necessary for this open-label study.

7.14.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the Investigator's Brochure.

7.14.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and

birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

8 CONDUCT OF THE TRIAL

8.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

8.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

8.3 Institutional Review Board / Ethics Committees

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

8.4 Schedule of Events

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See the Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include: blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium).

Hematology tests include: hemoglobin, hematocrit, complete blood count with differential and platelet count.

8.5 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity)
- Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

Cycle 1 Day 1:

- Collect any adverse events or new concomitant medications since Screening.
- Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP, and 12-lead ECG.
- Review results and confirm subject remains eligible for the study.
- Determine subject's starting dose based on the respective cohort mg/m^2 starting dose.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- Enroll subject for text message reminders if the subject consents to that service.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual

Cycle 1 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 4:

- Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.

Cycle 1 Day 8:

- Vital signs.
- Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8).

Cycle 2 (and any Dose Adjustment Cycle)

Repeat this visit as needed when dose adjustment is ongoing.

- Day 1:
  - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Take vital signs and perform physical examination (including weight).
  - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below.
  - If dosing will continue, dispense study medication.
  - Dispense calendar/diary.
  - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Day 8:
  - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Vital signs.
  - Collect pre-dose brequinar/DHO and hematology/chemistry samples.

- Perform bone marrow sampling for flow cytometry (window ±7 days).
- If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose.
- If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Continue to withhold study drug if safety remains unacceptable.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8).

Subjects may undergo dose adjustments at any time using the guidelines presented above. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects.

Dose adjustments are permitted throughout the study for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. This upper limit may be adjusted depending on safety/tolerability/DHO/brequinar PK or other factors during the study.

Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle.

In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow sampling as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks per the investigator's discretion.

A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response.

Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO and hematology/chemistry samples.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (note that bone marrow is collected at the C2D8 visit (window ±7 days), at Day 43, then every 12 weeks; only the Day 43 sample will be assessed for hematological toxicity).

- Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety).
- Dispense study medication.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.

Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (do not collect bone marrow if < 4 weeks since previous bone marrow sample obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

Follow Up Visit (2 weeks after Final Visit)

- Contact subject to elicit information about AEs/new concomitant medications since the last visit.

Survival information will be collected while the study is ongoing.

Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within four (4) weeks after the final dose.

8.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified window, it will not be necessary to file a protocol violation.

8.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

8.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

8.9 Short Messaging Service (SMS) Medication Reminders

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted in part to protect the security and privacy of protected health information (PHI). Covered entities (e.g., health care providers engaged in certain electronic transactions, health plans, and health care clearinghouses) that create, maintain, transmit, use, and disclose an individual's PHI are required to meet HIPAA requirements.

HIPAA's Privacy Rule restricts uses and disclosures of PHI, creates individual rights with respect to their PHI, and mandates administrative requirements. Among other requirements, the privacy rule requires a covered entity to reasonably safeguard PHI from any intentional or unintentional use or disclosure that is in violation of the requirements of HIPAA.

HIPAA's Security Rule requires covered entities to ensure confidentiality, integrity, and availability of its electronic PHI, to protect against reasonably anticipated threats or hazards to the security or integrity of its electronic PHI, to protect against reasonably anticipated impermissible uses and disclosure of its electronic PHI, and to ensure compliance by their workforce. Additionally, the Security Rule requires covered entities to put in place detailed administrative, physical, and technical safeguards to protect electronic PHI. To do this, covered entities are required to implement access controls and set up backup and audit controls for electronic PHI in a manner commensurate with the associated risk.

For protocol CCB-01, the Sponsor intends to utilize a third-party vendor with a HIPAA-compliant platform to send one-way text message reminders to study participants who have a mobile device. The SMS/text message will be sent on the days and times he or she is to take his or her study medication, e.g., Monday mornings and Thursday evenings. The exact timings of the reminders will be customized for each study participant. The PHI the third-party vendor receives will be restricted to the participant's mobile device number and study identification number. The study participant is not to reply to the text message except to "opt out" from the service by sending "STOP" in the message body. In any other case if he/she sends a text message, the texting service will reply with a message indicating that messages sent by participants are not being monitored. Study participants must agree to "opt in" for this service and can "opt out" at any time even if they initially agreed. Study participants will need to sign an addendum to the informed consent document documenting their decision prior to enrollment in the system (see Appendix 14.5).

The third-party vendor will sign an agreement with the Sponsor to use participant data only for the purposes of this study. Data will be purged from the vendor's servers at the conclusion of the trial upon written request by the Sponsor. Data will remain in the vendor's encrypted back-up files that will be maintained per HIPAA-compliant standards.

9 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs. Disease progression should not be reported as an AE unless worsening of signs and symptoms occur, or death from disease progression.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. If

the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.0* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

9.1 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

9.2 Classification of Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

9.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition ;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following a SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox@novellaclinical.com

MEDICAL MONITOR: **Robert Sims, MD**
E-mail: robert.sims@novellaclinical.com;
YYA36071medmon@novellaclinical.com
Telephone: 614-721-2630
24-hour safety line: 1-866-758-2798 or 919-313-7111
Fax: 206-826-0483

Sponsor Representative: **Barbara Powers, MSN, Ph.D.**
E-mail: bpowers@clearcreekbio.com
Telephone: 484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

9.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

9.5 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring

of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

9.6 Hematologic Adverse Events

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's

life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as ≥ Grade 4 neutropenia and/or thrombocytopenia, with a hypocellular bone marrow and no greater than 5% marrow blasts lasting for 2 weeks or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

9.7 Management of Myelosuppression

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh,, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

9.8 Differentiation Syndrome

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
    - Control of leukocytosis with hydroxyurea;
    - Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs,

continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated without dose reduction once the participant's clinical condition improves, upon discussion with the Sponsor.

9.9 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML for TLS from the international guidelines by Cairo et al., 2010 is as follows:

- Low risk disease: WBC $< 25 \times 10^9$ /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100 x 10^9 /L or WBC $< 25 \times 10^9$ /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100 x 10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008).
- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011)

- Figure 2 provides a flow chart for TLS monitoring.

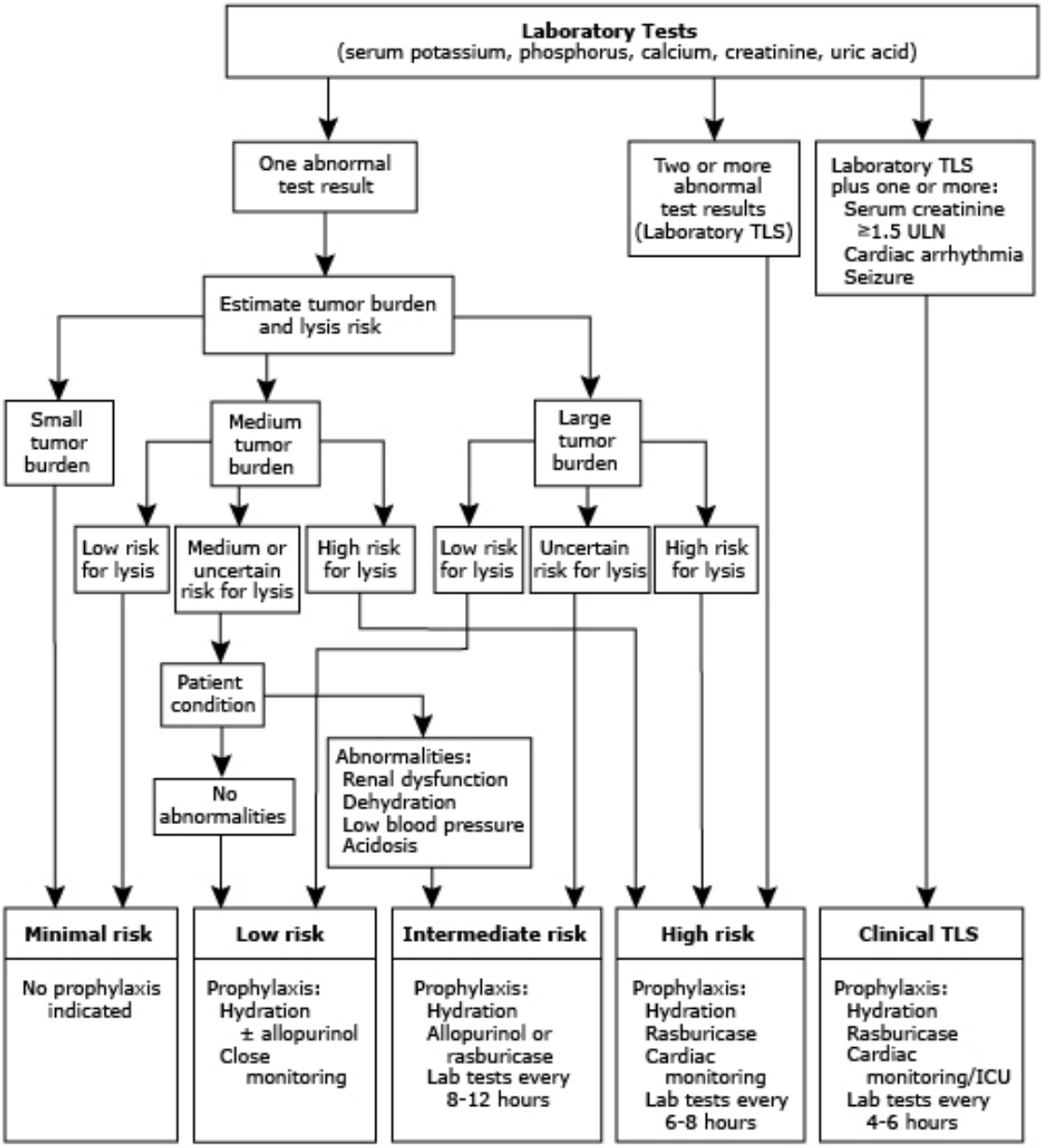

Figure 2. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

9.10 Infection Prophylaxis

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

9.11 Growth Factor Support

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

9.12 Management of Nausea, Vomiting, and Diarrhea

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

10 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

10.1 Study Populations for Analysis

The analysis sets are defined in Table 3.

Table 3. Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

10.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow

assessments will be summarized using appropriate descriptive statistics.

10.3 Efficacy Analyses

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 4 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 4. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses

	will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML will be assessed based on Döhner et al, 2017.

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

10.4 Other Endpoints

Brequinar Pharmacokinetics (PK)

Blood samples for PK analysis will be obtained at pre-specified times. Plasma PK parameters of brequinar including steady-state plasma concentration (Css); elimination half-life ($T_{1/2}$); Area under the concentration curve (AUC); systemic clearance (CL) and volume of distribution at steady state (Vss) will be estimated by compartmental and non-compartmental analysis (WinNonlin or similar).

Concentration data and PK parameters will be tabulated and summarized using descriptive

statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Blood samples for DHO analysis will be obtained at pre-specified times and will be summarized. Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

10.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting dose. An expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3.

10.6 Randomization

No randomization scheme is needed for this open label study.

10.7 Pooling of Study Centers

Not applicable to this small, early phase study.

10.8 Interim Analysis

No interim analysis is planned for this trial.

11 INVESTIGATOR RESPONSIBILITIES

11.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (page X) to indicate commitment to comply with the contents.

11.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 11.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

11.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

11.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

11.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or

of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

11.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

11.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

12 SPONSOR RESPONSIBILITIES

12.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change, or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

12.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

12.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

12.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

12.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

12.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

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14 APPENDICES

14.1 APPENDIX A: CCB-01 Schedule of Events

CCB-01 Schedule of Events	**Screen[b]**	**Cycle 1 (Study Days 1 – 14)**					**Dose Adjustment Cycle (Cycle 2 and beyond as needed)**		**Maintenance Dose Cycle (no dose adjustment) Every 2 weeks**	**Final Visit**	**F/U Phone Call**	**Survival**
Procedures[a]		**D1**	**D2**	**D3**	**D4**	**D8**	**D1**	**D8**	**D1**		**Final Visit + 2 wks**	
Informed Consent[b]	X											
AE/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Medical history[c]	X											
Demographics[d]	X											
Physical Exam[d]	X	X					X		X	X		
Vital Signs[d]	X	X				X	X	X	X	X		
Pregnancy Test[e]	X								X	X		
ECOG Performance Status	X											
Hematology/Chemistry	X	X				X	X	X	X	X		
Flow Cytometry[f]	X		X	X								
Chromosomal/mutational testing[g]	X											
12-lead ECG	X								X	X		
MUGA/Echocardiogram	X											
Bone Marrow Sampling[h]	X							X		X		
Brequinar/DHO Plasma Sample[i]		X	X	X	X	X	X	X	X	X		
Biobanking samples[j]	X								X	X		
Ship DHO Plasma Samples						X		X	X			
Dispense/Collect Study Medication		X					X		X	X		
Dispense/Collect Subject Calendar/Diary		X					X		X	X		
Survival Assessment												X

a. Visit window of ± 1 day for dose escalation cycles; window of ± 3 days for non dose escalation cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <72h since Screening assessment.
c. Medical history is to include AML diagnosis, previous AML treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Physical exam is to include weight.
e. For women of childbearing potential only.
f. Flow cytometry testing of peripheral blood is to be obtained at 0 (pre-dose C1D1), post dose 48 and 72 hours..
g. Testing panel is per institutional standard of care; obtain sample at Screening.
h. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. All bone marrow samples will be sent for biobanking from where further analysis can be done. Perform bone marrow sampling at screening, at study Day 22 (C2D8) with a window ±7 days, at Day 43, and once every 12 weeks after a stable dose has been reached. Timing of this procedure may be adjusted to ensure results are available for the next clinic visit.
i. Brequinar/DHO plasma sampling schedule: Cycle 1: 0 (pre-dose), post dose 1, 2, 4, 6, 24, 48, 72 hours and C1D8 pre-dose (+84h after C1D4 dose); Cycle 2 and adjustment cycles: pre-dose Days 1 and 8; every 2-week Maintenance Cycle until 3-months on drug: pre-dose Day 1 and every 2 to 4 week Maintenance Dose Cycle beyond 3-months on drug. Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Cycle 2 and beyond plasma brequinar/DHO draws ±4h. Ensure trough samples (e.g., C1D1, C2D1, C3D1) are obtained prior to dosing. Plasma samples for brequinar/DHO for expansion cohort are to be obtained prior to dosing on Day 1 of each 2-week cycle for the first 3 cycles, then every 12 weeks.
j. Biobanking samples (peripheral blood and bone marrow) are to be collected whenever bone marrow sampling is performed.

14.2 APPENDIX B: ECOG Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14.3 APPENDIX C: Brequinar/DHO Plasma Sampling

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Brequinar and DHO plasma samples are to be obtained at the following time points (±30 minutes through 6h, then ±2h for the 24h, 48h, 72h and 84h samples:

	Cycle 1									Cycle 2*		Maintenance Dose Cycle	Final Visit
	D1					D2	D 3	D 4	D8	D1	D8	D1	
Time Point	Pre-dose	1h	2h	4h	6h	24h	48h	72h	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose

*Or any cycle where the brequinar dose has been adjusted from the previous 2-week dose.

14.4 APPENDIX D: Common Terminology Criteria for Adverse Events (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

14.5 APPENDIX E: Sample Subject Consent Form

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 2.0 04June2018>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will take the study medication about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

Cycle 1 Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.

- Have a physical examination (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and still choose to participate, you will be given adequate study medication for 2 weeks (4 doses).
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Cycle 1 Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit. You will take your second dose of study medication this evening.
- **Cycle 1 Day 8**:

At this visit, you will:

- Have your vital signs checked.
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Take your next dose of study medication in the clinic.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.

Cycle 2

You will return to the clinic 2 weeks after starting the study medication. The study team may adjust your dose of study medication (you may be given more or less of the drug) depending on your safety results, laboratory, and DHO levels. This visit may be repeated as needed if your dose adjustment continues.

- **Day 1**:
  - Your unused study medication will be collected (if you have any), and your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
  - Your vital signs will be checked and a physical examination performed.

- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given adequate medication for another 2 weeks (4 doses). Take your next dose of study medication in the clinic.

● **Day 8:**

At this visit, you will:

- Have your vital signs checked.
- Have a bone marrow sample taken for flow cytometry (window ±7 days).
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will continue to take the medication dispensed to you.

<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)

Once you have reached a "stable dose" where no more dose adjustments seem to be needed, you will return to the clinic every 2 weeks and have the procedures below. After you've been taking the study medication for 3 months, your study doctor may space your visits out to every 4 weeks.

Day 1:

At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for pre-dose brequinar/DHO and hematology/chemistry.
- Have a physical examination, vital signs, urine pregnancy test for women able to bear children, 12-lead ECG.
- Have a bone marrow sampling (the bone marrow aspiration sampling is performed at study Day 22 ±7 days, at study Day 43 and repeated every 12 weeks or more often if there is a safety concern).
- Your study team will review the laboratory results/safety information and determine whether you should stay at the same dose or whether you should temporarily stop taking the study medication or whether the dose should be changed.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given additional medication and continue to take the medication dispensed to you as directed by the study team.
- Your diary/calendar will be collected and a new one provided to you.

<u>Final Visit</u>

This visit is to take place if you or your study team decide you should stop participation in the study or you have reached 12 months of study participation. At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for brequinar/DHO, flow cytometry and hematology/chemistry.
- Have a physical examination (including weight), vital signs, urine pregnancy test for women able to bear children, 12-lead ECG and bone marrow sampling (unless it has been less than 4 weeks since the previous bone marrow sampling).
- Turn in any unused study medication.
- Turn in your calendar/diary.

Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by phone to be asked about any new medical events or new or changed medications since your last clinic visit.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea
- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either

stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.
- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.
- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.
- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.
- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to

the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

Addendum to Informed Consent for Short Messaging Service (SMS/text)

Reminders for Protocol CCB-01

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Addendum ICF Version 1.0 31May2018>

WHY AM I BEING ASKED TO SIGN THIS ADDENDUM TO THE CONSENT?

You are being asked to sign this addendum to the consent because you have agreed to participant in study CCB-01 and because it is very important for you to take your study medication at the correct times (e.g., Monday mornings and Thursdays evenings). One effective way to help you remember to take your medication on time is for you to receive a text reminder on your phone. The sponsor of the study (Clear Creek Bio, Inc.) is using an external vendor to generate a text message reminder that will be sent to your mobile device when it is time for you to take your study medication.

VOLUNTARY NATURE OF THIS SERVICE

It is entirely optional for you to receive this service. Your decision to receive text message reminders for your medications will not in any way affect your ability to enroll in the study. You may also "opt out" at any time by responding "STOP" to the messages, or by contacting your study team.

DESCRIPTION OF THE NATURE OF THE DATA YOU WILL PROVIDE
You will provide your mobile device number to the study team who will then enter the number into the third-party vendor's system for sending out the text reminders.

DESCRIPTION OF HOW THE DATA WILL BE USED
The only information that will be shared with the third-party vendor is your mobile device number and your study participant identification number. The system is set up so that one-way messages are sent from the service to you. You should not reply to the messages you receive except to "opt out". If you do send a message, the texting service will reply with a message indicating that the messages you may send are not being monitored.

WHAT WILL THE MESSAGE SAY?
On the twice-weekly schedule (i.e., Monday mornings and Thursday evenings), you will receive a text with the following information: “It is time for you to take your CCB-01 study medication. Thank you for participating in this study.” You may delete this message after reading.

DESCRIPTION OF HOW THIS DATA WILL BE SECURELY MANAGED
The mobile device number you provide to be used for these reminders will be managed in a manner that ensures the best possible security. The mobile device number will not be shared with any other third-party vendor or the sponsor of this study (Clear Creek Bio, Inc.).

WHAT IF I DON’T HAVE A PHONE THAT CAN RECEIVE TEXT MESSAGES?
If you do not have a mobile phone or cannot receive text messages, you cannot participate in receiving these text message reminders.

DISCLOSURES OF RISKS AND VULNERABILITIES
Although unlikely, it is possible that the unencrypted text messages you receive could inadvertently be seen by someone else. Because the messages are de-identified (your name will not appear), the most information that could be seen would be that you are participating in a study. You are not sending any information back to the third-party vendor, so nothing you send could be seen by mistake.

The study team members are not responsible for any loss or breach of data that results from something beyond their control, e.g., you lose your mobile device containing text messages reminders, or a third-party vendor or host experiences a server/data breach.

Standard text/data messaging rates apply to these messages, and because some mobile phone providers charge an additional fee for the sending and receiving of text messages, you might be charged additionally by your mobile phone provider if you choose to receive the text message reminders.

PROCESS FOR NOTIFYING PARTICIPANT IN CASE OF AN ACTUAL OR POTENTIAL SECURITY BREACH

If the third-party vendor that has your mobile device number experiences a breach or a potential breach, the third-party vendor will notify the sponsor of this study, Clear Creek Bio, Inc. The sponsor will notify the study team at each participating institution, and the study team will contact you regarding the possible risks associated with the breach/potential breach regarding your mobile device number.

Consent Form SMS/Text Addendum Signature

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for receiving text message medication reminders for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary in this text messaging service and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the study team and third-party vendor to have access to my mobile device number.	
4. I agree to take part in the mobile device text message reminder for the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

APPENDIX F: WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health

care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat

to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

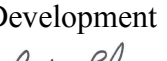
31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development  Digitally signed by Barbara L. Powers, MSN, PhD DN: cn=Barbara L. Powers, MSN, PhD, o=Clear Creek Bio, Inc., ou=Clinical Operations, email=bpowers@clearcreekbio.com, c=US Date: 2018.10.13 13:25:02 -04'00'	Date: 13 OCT 2018
PRINT NAME: Barbara L. Powers, MSN, Ph.D.	

Research & Development David P Hesson, PhD Digitally signed by David P Hesson, PhD Date: 2018.10.13 15:11:06 -04'00'	Date: 13 OCT 2018
PRINT NAME: David P. Hesson, Ph.D.	

Chemistry and Manufacturing/Quality David P. Hesson, PhD Digitally signed by David P. Hesson, PhD Date: 2018.10.13 15:11:58 -04'00'	Date: 13 OCT 2018
PRINT NAME: David P. Hesson, Ph.D.	

Sponsor Representative  Digitally signed by Vikram Sheel Kumar DN: cn=Vikram Sheel Kumar, o=Clear Creek Bio Inc., ou, email=kumar@clearcreekbio.com, c=US Date: 2018.10.13 15:03:49 -04'00'	Date: 13 Oct 2018
PRINT NAME: Vikram Sheel Kumar, MD	

Revision History/Amendments:

Version Number	Date
1.0	31 May 2018
2.0	04 June 2018
3.0	04 October 2018

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)

Study No: CCB-01

Version Date: 04 October 2018

Sponsor:

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IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal Dose$_{(10\%, 50\%, 90\%)}$
LPS	Lipopolysaccharide
M	Molar
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar

Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	• To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML.
Secondary Objectives	• To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. • To characterize the pharmacokinetic (PK) profile of brequinar. • To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. • To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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. Subject dosing will be adjusted based on safety/tolerability and DHO level. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each may be added if the Cohort 1 starting dose requires adjustment. Cohorts 2 and 3 may be expanded to 6 subjects using a 3 + 3 design if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the starting dose-adjustment part of the study, an expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated dose from Cohorts 1 – 3. Safety and tolerability will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs, bone marrow sampling, and adverse event reporting. Bone marrow sampling (bone marrow aspirate and core biopsy) will also be utilized for efficacy. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	• Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	• Rates of treatment-emergent adverse events. • Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. • Event free survival (EFS). • Duration of response. • PK profile of brequinar. • DHO plasma profile.
Exploratory endpoints:	• 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.
Sample Size:	Up to 27 subjects
Number of	3 – 5

Sites:	
Study Period:	An enrollment period of 18 - 24 months is expected.

Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial.
	2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification who have exhausted available therapy.
	3. ECOG Performance Status 0 to 2.
	4. Cardiac ejection fraction ≥ 40%
	5. Adequate hepatic function (unless deemed to be related to underlying leukemia).
	    1. Direct bilirubin ≤ 2 x ULN
	    2. ALT ≤ 3 x ULN
	    3. AST ≤ 3 x ULN
	6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
	7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
	8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
	9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to

	meet this criterion). 3. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 4. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 6. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome. 7. AML relapse less than 6 months following stem cell transplantation. 8. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 9. Active cerebrospinal involvement of AML. 10. Diagnosis of acute promyelocytic leukemia (APL) 11. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 12. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 13. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 14. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

Treatment	Subjects will self-administer oral brequinar twice weekly (every 84 hours +/- 6 hours). Treatment cycles will be 2 weeks. Visits will take place at least every 2 weeks through 3 months; visits thereafter will be every 2 – 4 weeks at the discretion of the investigator at each site. Inter-cohort and intra-subject dose adjustments may occur throughout the study as outlined in the sections below. Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: - Demographics (height, weight, date of birth, gender, race, ethnicity) - Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) - Concomitant medications. - Physical examination (including weight). - Vital signs (heart rate, respiratory rate, blood pressure, body temperature). - Pregnancy test for women of childbearing potential (WOCBP) - ECOG performance assessment. - Hematology/chemistry. - 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function. - Bone marrow sampling - Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. **Cycle 1 Day 1:** - Collect any adverse events or new concomitant medications since Screening. - Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. - Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP and 12-lead ECG. - Review results and confirm subject remains eligible for the study. - Determine subject's starting dose based on the respective cohort mg/m^2 starting dose. - Dispense study medication.

	– Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. – Enroll subject for text message reminders if the subject consents to that service. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 2**: – Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 3**: – Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 4**: – Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. **Cycle 1 Day 8**: – Vital signs. – Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Notify DHO assay laboratory of incoming shipment and ship Cycle 1

	brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8). **<u>Cycle 2 (and any Dose Adjustment Cycle)</u>** Repeat this visit as needed whenever any dose adjustment is required. **Day 1:** - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Take vital signs and perform physical examination (including weight). - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples. - Process and store brequinar/DHO samples per the supplied laboratory manual. - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below. - If dosing will continue, dispense study medication. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) **Day 8:** - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Vital signs. - Collect pre-dose brequinar/DHO and hematology/chemistry samples. - Perform bone marrow sampling for flow cytometry (window ±7 days). - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose. - Process and store brequinar/DHO samples per the supplied laboratory manual. - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose. - Continue to withhold study drug if safety remains unacceptable. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) - Notify DHO assay laboratory of incoming shipment and ship

	brequinar/DHO samples (samples from current cycle's Days 1 and 8). Subjects may undergo dose adjustments at any time using the guidelines presented in Section 7 of the protocol. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2, with the exception of Cohort 1 subjects who may not escalate above the 500 mg/m^2 starting dose. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects. Dose adjustments are permitted throughout the study (except for the restriction of no escalation in Cohort 1) for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. **<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)** Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle. In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow aspiration as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks (visit interval at the investigator's discretion). A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response (Figure 1). **Day 1:** - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Collect pre-dose brequinar/DHO and hematology/chemistry samples. - Conduct physical examination, vital signs, urine pregnancy test for WOCBP 12-lead ECG and bone marrow sampling (note that bone marrow is collected on study Day 22 (C2D8 ± 7 days), at Day 43, and then every 12 weeks; the Day 43 sample will be assessed for hematological toxicity). - Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety). - Dispense study medication. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study

<table>
<tr><td></td><td>medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
Final Visit
This visit is to take place when a subject is discontinuing from the study.
- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP (if ≥4 weeks since previous), 12-lead ECG (if ≥4 weeks since previous), and bone marrow sampling (if > 12 weeks since previous bone marrow sample obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

Follow Up Visit (2 weeks after Final Visit)
- Contact subject to elicit information about AEs/new concomitant medications since the last visit.
Survival information will be collected while the study is ongoing.
Unscheduled Visits
Unscheduled visits and tests to assess AEs are permitted as needed.</td></tr>
<tr><td>Safety/
Tolerability</td><td>Safety/Tolerability – Subject Level
Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.
Exceptions to Grade 3 Nonhematologic AEs
<table>
<tr><th>Condition</th><th>Exception Description</th></tr>
<tr><td>Nausea/
Emesis</td><td>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.</td></tr>
<tr><td>Diarrhea</td><td>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.</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Fatigue</td><td>Grade 3 fatigue lasting less than 1 week.</td></tr><tr><td>Laboratory abnormalities</td><td>Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.</td></tr></table> **Hematologic Toxicity** After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit. **Safety/Tolerability – Cohort Level** Acceptable safety/tolerability at the cohort level is defined below: a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose. b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. Upon cohort expansion to 6 subjects, if a total of ≤2 out of 6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
Cohort Starting Doses	Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety. After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1. If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are

	not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit. See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.
Expansion Cohort	Once a dose has been reached that has adequate DHO level and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions about adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects may also undergo individual dose adjustment. See Section 7.3.3 for the expansion cohort safety rules.
Individual Dose Adjustment Guidelines	With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be escalated, maintained (stable dose), held then reduced, or discontinued. The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned. As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred. Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO level (with the exception of no escalation for Cohort 1 subjects). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced. Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels and bone marrow results have been reviewed. Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose

<table>
<tr><td></td><td>adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

The intrasubject dose-adjustment criteria are presented below.

Intra-subject Dose Adjustment Criteria*
<table>
<tr><th>Acceptable Safety/Tolerability? (see safety definition above)</th><th>Adequate DHO Level?</th><th>Planned Intra-Subject Dose Adjustment</th></tr>
<tr><td>Yes</td><td>Yes</td><td>Maintain; continue at same dose.</td></tr>
<tr><td>Yes</td><td>No</td><td>Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.</td></tr>
<tr><td>No</td><td>Regardless of DHO</td><td>Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week.
If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.</td></tr>
<tr><td colspan="3">*Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.</td></tr>
</table></td></tr>
<tr><td>Brequinar/DHO</td><td>Plasma brequinar/DHO samples are to be obtained for each subject for the first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to subjects in the expansion cohort who will have trough sampling only prior to the start of each two-week cycle.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour post dose brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.</td></tr>
<tr><td>Statistical Analysis</td><td>A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For</td></tr>
</table>

	qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death

	• Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

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2 INTRODUCTION

2.1 Background: Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10%.[1] It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

2.2 Dihydroorotate dehydrogenase (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous enzyme, and lack of its level is not compatible with life. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

2.3 Brequinar

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s,

which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was

reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

2.4 Rationale for the Planned Trial

This study is designed to obtain safety and efficacy data for brequinar in patients with AML.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in more detail in Section 7.5.

2.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-a-week administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a biweekly schedule of brequinar dosed approximately every 84 hours, while measuring plasma DHO to fine-tune the dosing schedule that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see Brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggest that a starting dose for Cohort 1 of 500 mg/m^2 p.o. will be safe and well-tolerated in subjects with AML. Each subject's subsequent dosing may be adjusted depending on the safety, tolerability and DHO level obtained during the period following dose adjustment. Each of the two planned subsequent cohorts may also have an adjusted starting dose, again depending on safety, tolerability and DHO level observed in previous cohorts. See Section 7.4.

2.5 Risk/Benefit of Brequinar

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of AML is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment in patients with AML is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with AML typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

2.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of

these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the guidelines presented in Section 9.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and treatment are described in Sections 9.10 and 9.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 9.7.

2.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

2.7.1 CYP Interactions

No formal drug-drug interaction studies have been performed with medications commonly used in treating AML. The nonclinical studies have demonstrated there is no first-pass metabolism, and there have been no apparent hepatotoxic effects in the clinical studies performed to date.

2.8 Steps to be Taken to Control or Mitigate Risks

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 9.

3 TRIAL OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML.

3.2 Secondary Objectives

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

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

4 TRIAL DESIGN

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 may be adjusted based on safety/tolerability and DHO level.

Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting doses. Cohorts 2 and 3 may be expanded to 6 subjects if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the cohort dose-adjustment part of the study, an expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized for efficacy. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in more detail in Section 7.

5 TRIAL ENDPOINTS

5.1 Primary Endpoint

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

5.2 Secondary Endpoints

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

5.3 Exploratory Endpoints

- 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

6 TRIAL POPULATION

6.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

6.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial.
2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification who have exhausted available therapy.
3. ECOG Performance Status 0 to 2.
4. Cardiac ejection fraction $\geq 40\%$
5. Adequate hepatic function (unless deemed to be related to underlying leukemia)
    a. Direct bilirubin ≤ 2 x ULN
    b. ALT ≤ 3 x ULN
    c. AST ≤ 3 x ULN
6. Adequate renal function as documented by creatinine clearance $\geq$ 30 mL/min based on the Cockcroft-Gault equation.
7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

6.3 Exclusion Criteria

1. Patients in need of immediate leukapheresis are excluded.
2. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to meet this criterion).

3. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.
4. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.
5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:
    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.
    b. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.
6. AML relapse less than 6 months following stem cell transplantation.
7. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).
8. Active cerebrospinal involvement of AML.
9. Diagnosis of acute promyelocytic leukemia (APL).
10. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.
11. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.
12. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
13. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

6.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

7 STUDY TREATMENTS

Subjects will self-administer oral brequinar twice weekly (approximately every 84 hours). Treatment cycles will be 2 weeks. Dose adjustment is to occur as outlined below. Visits will take place at least every 2 weeks through 3 months. More frequent visits are permitted to assess and/or treat adverse events. Less frequent visits (up to 4-week intervals) are permitted after 3 months depending on subject safety/tolerability and response. Cohort 1 will begin at 500 mg/m^2 twice weekly. Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose, but the intra-subject dose may be reduced if unacceptable safety occurs. Subsequent cohorts will have a starting dose that may be adjusted based on the safety/tolerability (Section 7.3.1, Section 7.3.2) and DHO levels of the previous cohort. The dosing for individual subjects may be adjusted based on the safety/tolerability and DHO levels as shown in Section 7.5.

7.1 Description of Brequinar:

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis based on the starting dose of a subject's cohort and the tolerability, safety and DHO level assessed following each dose. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 8 hours after the missed dose. If more than 8 hours have elapsed or if the dose was vomited or if the subject for any reason is unable to take the scheduled dose within 8 hours, omit that dose, and the subject should resume treatment with the next scheduled dose. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

7.2 Treatment Administration

Subjects will take oral brequinar twice weekly (approximately every 3.5 days) e.g., Monday morning and Thursday evening. Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar brequinar/DHO samples. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

7.3 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). After completion of Cohort 1 (which will have a fixed starting dose of 500 mg/m^2 with no dose escalation permitted), safety/tolerability will be used to determine both cohort starting doses for subsequent cohorts and individual dosing adjustments. Safety at the subject level is defined in Section 7.3.1; hematologic toxicity is defined in Section 7.3.1.1; and safety at the cohort level is defined in Section 7.4.

7.3.1 Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting

during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in Table 1.

Table 1. Exceptions to Grade 3 Nonhematologic AEs

Condition	Exception Description
Nausea/ Emesis	Grade 3 nausea and/or emesis resolving 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 ≤ Grade 1 or baseline within 1 week after receiving the maximal supportive therapy based on standard practice.
Fatigue	Grade 3 fatigue lasting less than 1 week.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.

7.3.1.1 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

7.3.2 Safety/Tolerability – Cohort Level

Acceptable safety/tolerability at the cohort level is defined below:

a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. If a total of ≤2 out of 6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.

7.3.3 Safety/Tolerability – Expansion Cohort

The safety and tolerability of the starting dose for the Expansion Cohort will have been determined during the Cohort Level adjustments defined in the preceding section. If >1 of the first 5 subjects in the Expansion Cohort cannot tolerate this starting dose based on the rules for safety and tolerability at the subject level (Section 7.3.1), the starting dose for the next cohort will be reduced by 75 mg/m^2. If >1 of the second 5 subjects cannot tolerate the reduced starting dose, the starting dose will be again reduced by 75 mg/m^2 for the final 5 subjects planned for this cohort. All of these subjects are eligible for intra-subject dose adjustment and will follow the same individual subject safety rules for either stopping dosing or dose adjustment as presented in Section 7.3.1 and Section 7.5.

7.4 Cohort Starting Doses

Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety.

After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1.

If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit.

See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.

7.5 Individual Dose Adjustment Guidelines

With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be adjusted from the starting dose by being escalated, maintained (stable dose), held then reduced, or discontinued (except in Cohort 1 where subjects' doses may not be escalated beyond the 500 mg/m^2 starting dose). The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned. As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO levels (except in Cohort 1). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels, and bone marrow results have been reviewed.

7.5.1 DHO Threshold

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

Table 2 and Figure 1 present the intra-subject dose-adjustment criteria. Note that there is no dose escalation in Cohort 1.

Table 2. Intra-Subject Dose Adjustment*

Acceptable Safety/Tolerability? (see safety definition above)	**Adequate DHO Level?**	**Planned Intra-Subject Dose Adjustment**
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.

* Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.

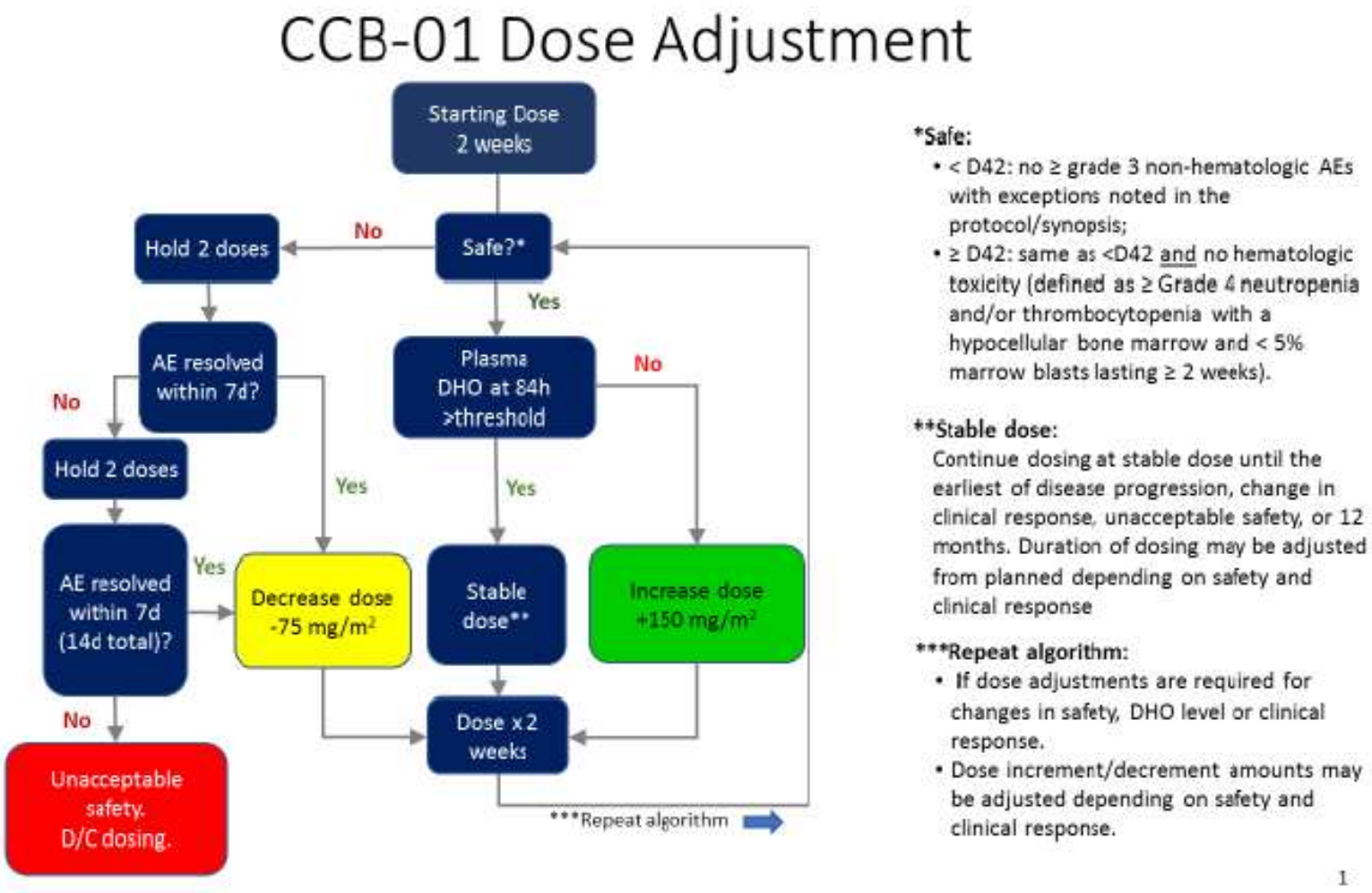

Figure 1. Dose Adjustment – Subject Level

7.6 Medication/AE Diary

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

7.7 Bone Marrow Biopsy

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the C2D8 visit ± 7 days, and one at Day 43 ± 7 days; thereafter, bone marrow sampling will be every 12 weeks and at the Final Visit. If a participant develops frank evidence of progression of AML during the course of treatment based on laboratory or clinical assessment, then he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at the Day 43 visit, then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for the Day 43 visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

7.8 Flow Cytometry

Peripheral blood samples are to be obtained for flow cytometry in Cycle 1 at baseline (Day 1 pre-dose), Day 2, and Day 3

7.9 Expansion Cohort

Once a dose has been reached that has adequate DHO level (as mentioned above, “adequate” trough DHO may be adjusted after reviewing DHO level, safety and clinical response data), and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions regarding adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects are eligible for intra-subject dose adjustment (see Section 7.3.1 and Section 7.5).

The expansion cohort will follow the same visit procedures as the Maintenance Dose cohort and visit frequency may vary from 2 to 4 weeks.

7.10 Study Drug Discontinuation

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh), the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued

if there is evidence of unacceptable safety/tolerability that does not resolve within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 30 days after the last dose of brequinar or until they receive another treatment for their AML. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

7.11 Brequinar Pharmacokinetics (PK) / Dihydroorotate (DHO) Plasma Levels

Plasma samples for brequinar/DHO levels are to be obtained for each subject for the subject's first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is baseline at 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to Cycle 1 for subjects in the expansion cohort, see below.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84h}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.

Directions regarding sample processing are presented in a separate laboratory manual.

7.12 Concomitant Medication/Treatment

The name, start date (if known), indication for use and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;
- Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.

7.12.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

7.13 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

7.14 Storage, Stability, Labeling and Packaging

7.14.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

7.14.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-01

Contents: 100 or 250 mg capsules

For oral use only. Take with approximately 8 ounces water every 3.5 days.

Subject Number: XX-XXXX

Treatment Duration: As directed

IND: 138355 Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

7.14.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution. No randomization codes are necessary for this open-label study.

7.14.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the Investigator's Brochure.

7.14.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the

next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

8 CONDUCT OF THE TRIAL

8.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

8.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

8.3 Institutional Review Board / Ethics Committees

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

8.4 Schedule of Events

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 14.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include: blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium).

Hematology tests include: hemoglobin, hematocrit, complete blood count with differential and platelet count.

8.5 Study Conduct

8.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity).
- Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

8.5.2 Cycle 1

Cycle 1 Day 1:

- Collect any adverse events or new concomitant medications since Screening.
- Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP, and 12-lead ECG.
- Review results and confirm subject remains eligible for the study.
- Determine subject's starting dose based on the respective cohort mg/m^2 starting dose.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- Enroll subject for text message reminders if the subject consents to that service.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual

Cycle 1 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 4:

- Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.

Cycle 1 Day 8:

- Vital signs.
- Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8).

8.5.3 Cycle 2 (and any Dose Adjustment Cycle)

Repeat this visit as needed when dose adjustment is ongoing.

- Day 1:
  - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Take vital signs and perform physical examination (including weight).
  - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below.
  - If dosing will continue, dispense study medication.
  - Dispense calendar/diary.

- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)

- Day 8:
  - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Vital signs.
  - Collect pre-dose brequinar/DHO and hematology/chemistry samples.
  - Perform bone marrow sampling (window ±7 days).
  - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose.
  - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Continue to withhold study drug if safety remains unacceptable.
  - Dispense calendar/diary.
  - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
  - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8).

Subjects may undergo dose adjustments at any time using the guidelines presented above. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects.

Dose adjustments are permitted throughout the study for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. This upper limit may be adjusted depending on safety/tolerability/DHO/brequinar PK or other factors during the study.

8.5.4 Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle.

In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow sampling as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks per the investigator's discretion.

A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response.

Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO and hematology/chemistry samples.
- Conduct physical examination vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (note that bone marrow is collected at the C2D8 visit (window ±7 days), at Day 43, then every 12 weeks; the Day 43 sample will be assessed for hematological toxicity).
- Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety).
- Dispense study medication.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.

8.5.5 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (do not collect bone marrow if < 4 weeks since previous bone marrow sample obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

8.5.6 Follow Up Visit (2 weeks after Final Visit)

- Contact subject to elicit information about AEs/new concomitant medications since the last visit. Survival information will be collected while the study is ongoing.

8.5.7 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within four (4) weeks after the final dose.

8.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified window, it will not be necessary to file a protocol violation.

8.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

8.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

8.9 Short Messaging Service (SMS) Medication Reminders

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted in part to protect the security and privacy of protected health information (PHI). Covered entities (e.g., health care providers engaged in certain electronic transactions, health plans, and health care clearinghouses) that create, maintain, transmit, use, and disclose an individual's PHI are required to meet HIPAA requirements.

HIPAA's Privacy Rule restricts uses and disclosures of PHI, creates individual rights with respect to their PHI, and mandates administrative requirements. Among other requirements, the privacy rule requires a covered entity to reasonably safeguard PHI from any intentional or unintentional use or disclosure that is in violation of the requirements of HIPAA.

HIPAA's Security Rule requires covered entities to ensure confidentiality, integrity, and availability of its electronic PHI, to protect against reasonably anticipated threats or hazards to the security or integrity of its electronic PHI, to protect against reasonably anticipated impermissible uses and disclosure of its electronic PHI, and to ensure compliance by their workforce. Additionally, the Security Rule requires covered entities to put in place detailed administrative, physical, and technical safeguards to protect electronic PHI. To do this, covered entities are required to implement access controls and set up backup and audit controls for electronic PHI in a manner commensurate with the associated risk.

For protocol CCB-01, the Sponsor intends to utilize a third-party vendor with a HIPAA-compliant platform to send one-way text message reminders to study participants who have a mobile device. The SMS/text message will be sent on the days and times he or she is to take his or her study medication, e.g., Monday mornings and Thursday evenings. The exact timings of the reminders will be customized for each study participant. The PHI the third-party vendor receives will be restricted to the participant's mobile device number and study identification number. The study participant is not to reply to the text message except to "opt out" from the service by sending "STOP" in the message body. In any other case if he/she sends a text message, the texting service will reply with a message indicating that messages sent by participants are not being monitored. Study participants must agree to "opt in" for this service and can "opt out" at any time even if they initially agreed. Study participants will need to sign an addendum to the informed consent document documenting their decision prior to enrollment in the system (see Appendix 14.5).

The third-party vendor will sign an agreement with the Sponsor to use participant data only for the purposes of this study. Data will be purged from the vendor's servers at the conclusion of the trial upon written request by the Sponsor. Data will remain in the vendor's encrypted back-up files that will be maintained per HIPAA-compliant standards.

9 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs. Disease progression should not be reported as an AE unless worsening of signs and symptoms occur, or death from disease progression.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. If

the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.0* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

9.1 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

9.2 Classification of Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

9.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition ;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following a SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox@novellaclinical.com

MEDICAL MONITOR: **Robert Sims, MD**
E-mail: robert.sims@novellaclinical.com;
YYA36071medmon@novellaclinical.com
Telephone: 614-721-2630
24-hour safety line: 1-866-758-2798 or 919-313-7111
Fax: 206-826-0483

Sponsor Representative: **Barbara Powers, MSN, Ph.D.**
E-mail: bpowers@clearcreekbio.com
Telephone: 484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

9.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

9.5 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug.

Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

9.6 Hematologic Adverse Events

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be

considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

9.7 Management of Myelosuppression

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

9.8 Differentiation Syndrome

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
    - Control of leukocytosis with hydroxyurea;

- Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs, continued for a minimum of 3 days;
- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated without dose reduction once the participant's clinical condition improves, upon discussion with the Sponsor.

9.9 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC < 25 x 10^9 /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100 x 10^9 /L or WBC < 25 x 10^9 /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100 x 10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).
- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 2 provides a flow chart for TLS monitoring.

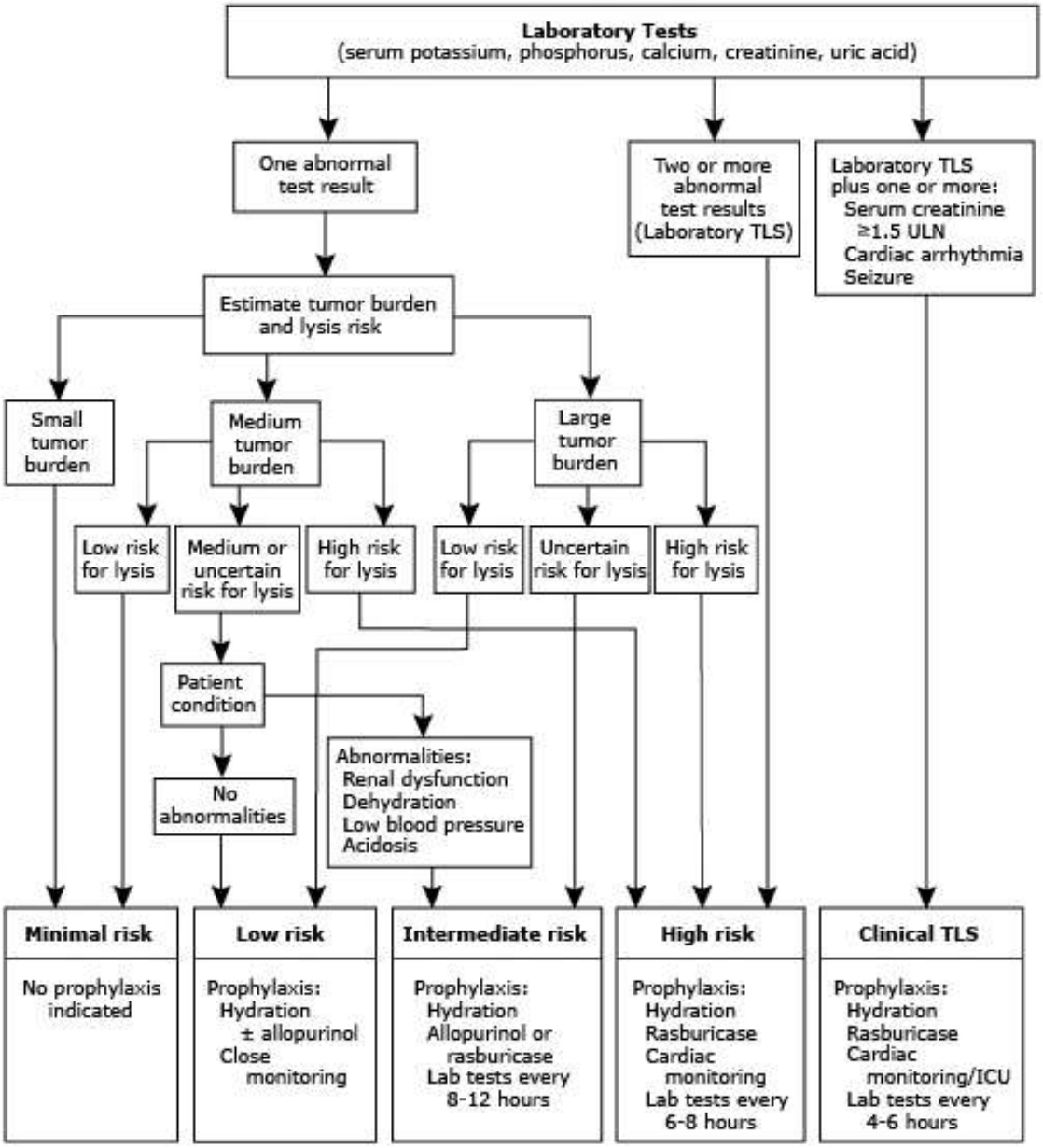

Figure 2. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

9.10 Infection Prophylaxis

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

9.11 Growth Factor Support

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

9.12 Management of Nausea, Vomiting, and Diarrhea

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

10 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

10.1 Study Populations for Analysis

The analysis sets are defined in Table 3.

Table 3. Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

10.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

10.3 Efficacy Analyses

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 4 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 4. Efficacy Analyses

Endpoint	**Statistical Analysis Methods**
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for

	time-to-event endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

10.4 Other Endpoints

Brequinar Pharmacokinetics (PK)

Blood samples for PK analysis will be obtained at pre-specified times. Plasma PK parameters of brequinar including steady-state plasma concentration (Css); elimination half-life ($T_{1/2}$); Area under the concentration curve (AUC); systemic clearance (CL) and volume of distribution at steady state (Vss) will be estimated by compartmental and non-compartmental analysis (WinNonlin or similar).

Concentration data and PK parameters will be tabulated and summarized using descriptive

statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Blood samples for DHO analysis will be obtained at pre-specified times and will be summarized. Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

10.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting dose. The cohorts with 3 subjects may be expanded to 6 subjects depending on safety outcomes within the cohort. An expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3.

10.6 Randomization

No randomization scheme is needed for this open label study.

10.7 Pooling of Study Centers

Not applicable to this small, early phase study.

10.8 Interim Analysis

No interim analysis is planned for this trial.

11 INVESTIGATOR RESPONSIBILITIES

11.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 14.6) to indicate commitment to comply with the contents.

11.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 11.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

11.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being

evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

11.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

11.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to

the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

11.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

11.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

12 SPONSOR RESPONSIBILITIES

12.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

12.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

12.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

12.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

12.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

12.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

13 REFERENCES

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14 APPENDICES

14.1 APPENDIX A: CCB-01 Schedule of Events

CCB-01 Schedule of Events	**Screen[b]**	**Cycle 1 (Study Days 1 – 14)**					**Dose Adjustment Cycle (Cycle 2 and beyond as needed)**		**Maintenance Dose Cycle (no dose adjustment) Every 2 weeks**	**Final Visit**	**F/U Phone Call**	**Survival**
Procedures[a]		**D1**	**D2**	**D3**	**D4**	**D8**	**D1**	**D8**	**D1**		**Final Visit + 2 wks**	
Informed Consent[b]	X											
AE/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Medical history[c]	X											
Demographics[d]	X											
Physical Exam[d]	X	X					X		X	X		
Vital Signs[d]	X	X				X	X	X	X	X		
Pregnancy Test[e]	X								X	X		
ECOG Performance Status	X											
Hematology/Chemistry	X	X				X	X	X	X	X		
Flow Cytometry[f]			X	X								
Chromosomal/mutational testing[g]	X											
12-lead ECG	X								X	X		
MUGA/Echocardiogram	X											
Bone Marrow Sampling[h]	X							X		X		
Brequinar/DHO Plasma Sample[i]		X	X	X	X	X	X	X	X	X		
Biobanking samples[j]	X								X	X		
Ship DHO Plasma Samples						X		X	X			
Dispense/Collect Study Medication		X					X		X	X		
Dispense/Collect Subject Calendar/Diary		X					X		X	X		
Survival Assessment												X

a. Visit window of ± 1 day for dose escalation cycles; window of ± 3 days for non dose escalation cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <72h since Screening assessment.
c. Medical history is to include AML diagnosis, previous AML treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Physical exam is to include weight.
e. For women of childbearing potential only.
f. Flow cytometry testing of peripheral blood is to be obtained at 0 (pre-dose C1D1), post dose 48 and 72 hours.
g. Testing panel is per institutional standard of care; obtain sample at Screening.
h. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking further analysis. Perform bone marrow sampling at screening, at study Day 22 (C2D8), at Day 43, and once every 12 weeks after a stable dose has been reachedTiming of this procedure may be adjusted to ensure results are available for the next clinic visit.
i. Brequinar/DHO plasma sampling schedule: Cycle 1: 0 (pre-dose), post dose 1, 2, 4, 6, 24, 48, 72 hours and C1D8 pre-dose (+84h after C1D4 dose); Cycle 2 and adjustment cycles: pre-dose Days 1 and 8; every 2-week Maintenance Cycle until 3-months on drug: pre-dose Day 1 and every 2 to 4 week Maintenance Dose Cycle beyond 3-months on drug. Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Cycle 2 and beyond plasma brequinar/DHO draws ±4h. Ensure trough samples (e.g., C1D1, C2D1, C3D1) are obtained prior to dosing. Plasma samples for brequinar/DHO for expansion cohort are to be obtained prior to dosing on Day 1 of each 2-week cycle for the first 3 cycles, then every 12 weeks.
j. Biobanking samples (bone marrow) are to be collected whenever bone marrow sampling is performed.

14.2 APPENDIX B: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14.3 APPENDIX C: Brequinar/DHO Plasma Sampling

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Brequinar and DHO plasma samples are to be obtained at the following time points (±30 minutes through 6h, then ±2h for the 24h, 48h, 72h and 84h samples:

	Cycle 1									Cycle 2*		Maintenance Dose Cycle	Final Visit
	D1					D2	D 3	D 4	D8	D1	D8	D1	
Time Point	Pre-dose	1h	2h	4h	6h	24h	48h	72h	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose

*Or any cycle where the brequinar dose has been adjusted from the previous 2-week dose.

14.4 APPENDIX D: Common Terminology Criteria for Adverse Events (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

14.5 APPENDIX E: Sample Subject Consent Form

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 2.0 04June2018>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will take the study medication about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

<u>Cycle 1 Day 1:</u>

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.

- Have a physical examination (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and still choose to participate, you will be given adequate study medication for 2 weeks (4 doses).
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Cycle 1 Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit. You will take your second dose of study medication this evening.
- **Cycle 1 Day 8**:

At this visit, you will:

- Have your vital signs checked.
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Take your next dose of study medication in the clinic.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.

Cycle 2

You will return to the clinic 2 weeks after starting the study medication. The study team may adjust your dose of study medication (you may be given more or less of the drug) depending on your safety results, laboratory, and DHO levels. This visit may be repeated as needed if your dose adjustment continues.

- **Day 1**:

- Your unused study medication will be collected (if you have any), and your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- Your vital signs will be checked and a physical examination performed.
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given adequate medication for another 2 weeks (4 doses). Take your next dose of study medication in the clinic.

● **Day 8:**

At this visit, you will:

- Have your vital signs checked.
- Have a bone marrow sample taken for flow cytometry (window ±7 days).
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will continue to take the medication dispensed to you.

<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)

Once you have reached a "stable dose" where no more dose adjustments seem to be needed, you will return to the clinic every 2 weeks and have the procedures below. After you've been taking the study medication for 3 months, your study doctor may space your visits out to every 4 weeks.

Day 1:

At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for pre-dose brequinar/DHO and hematology/chemistry.
- Have a physical examination, vital signs, urine pregnancy test for women able to bear children, 12-lead ECG.
- Have a bone marrow sampling (the bone marrow aspiration sampling is performed at study Day 22 ±7 days, at study Day 43 and repeated every 12 weeks or more often if there is a safety concern).
- Your study team will review the laboratory results/safety information and determine whether you should stay at the same dose or whether you should temporarily stop taking the study medication or whether the dose should be changed.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given additional medication and continue to take the medication dispensed to you as directed by the study team.
- Your diary/calendar will be collected and a new one provided to you.

Final Visit

This visit is to take place if you or your study team decide you should stop participation in the study or you have reached 12 months of study participation. At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for brequinar/DHO, flow cytometry and hematology/chemistry.
- Have a physical examination (including weight), vital signs, urine pregnancy test for women able to bear children, 12-lead ECG and bone marrow sampling (unless it has been less than 4 weeks since the previous bone marrow sampling).
- Turn in any unused study medication.
- Turn in your calendar/diary.

Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by phone to be asked about any new medical events or new or changed medications since your last clinic visit.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea
- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.
- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.
- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.
- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.
- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

_____	_____	_____	_____
Printed Name of Subject	Signature of Subject	Date	**Time**
_____	_____	_____	_____
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

Addendum to Informed Consent for Short Messaging Service (SMS/text)

Reminders for Protocol CCB-01

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Addendum ICF Version 1.0 31May2018>

WHY AM I BEING ASKED TO SIGN THIS ADDENDUM TO THE CONSENT?

You are being asked to sign this addendum to the consent because you have agreed to participant in study CCB-01 and because it is very important for you to take your study medication at the correct times (e.g., Monday mornings and Thursdays evenings). One effective way to help you remember to take your medication on time is for you to receive a text reminder on your phone. The sponsor of the study (Clear Creek Bio, Inc.) is using an external vendor to generate a text message reminder that will be sent to your mobile device when it is time for you to take your study medication.

VOLUNTARY NATURE OF THIS SERVICE

It is entirely optional for you to receive this service. Your decision to receive text message reminders for your medications will not in any way affect your ability to enroll in the study. You may also "opt out" at any time by responding "STOP" to the messages, or by contacting your study team.

DESCRIPTION OF THE NATURE OF THE DATA YOU WILL PROVIDE
You will provide your mobile device number to the study team who will then enter the number into the third-party vendor's system for sending out the text reminders.

DESCRIPTION OF HOW THE DATA WILL BE USED
The only information that will be shared with the third-party vendor is your mobile device number and your study participant identification number. The system is set up so that one-way messages are sent from the service to you. You should not reply to the messages you receive except to "opt out". If you do send a message, the texting service will reply with a message indicating that the messages you may send are not being monitored.

WHAT WILL THE MESSAGE SAY?
On the twice-weekly schedule (i.e., Monday mornings and Thursday evenings), you will receive a text with the following information: “It is time for you to take your CCB-01 study medication. Thank you for participating in this study.” You may delete this message after reading.

DESCRIPTION OF HOW THIS DATA WILL BE SECURELY MANAGED
The mobile device number you provide to be used for these reminders will be managed in a manner that ensures the best possible security. The mobile device number will not be shared with any other third-party vendor or the sponsor of this study (Clear Creek Bio, Inc.).

WHAT IF I DON’T HAVE A PHONE THAT CAN RECEIVE TEXT MESSAGES?
If you do not have a mobile phone or cannot receive text messages, you cannot participate in receiving these text message reminders.

DISCLOSURES OF RISKS AND VULNERABILITIES
Although unlikely, it is possible that the unencrypted text messages you receive could inadvertently be seen by someone else. Because the messages are de-identified (your name will not appear), the most information that could be seen would be that you are participating in a study. You are not sending any information back to the third-party vendor, so nothing you send could be seen by mistake.

The study team members are not responsible for any loss or breach of data that results from something beyond their control, e.g., you lose your mobile device containing text messages reminders, or a third-party vendor or host experiences a server/data breach.

Standard text/data messaging rates apply to these messages, and because some mobile phone providers charge an additional fee for the sending and receiving of text messages, you might be charged additionally by your mobile phone provider if you choose to receive the text message reminders.

PROCESS FOR NOTIFYING PARTICIPANT IN CASE OF AN ACTUAL OR POTENTIAL SECURITY BREACH

If the third-party vendor that has your mobile device number experiences a breach or a potential breach, the third-party vendor will notify the sponsor of this study, Clear Creek Bio, Inc. The sponsor will notify the study team at each participating institution, and the study team will contact you regarding the possible risks associated with the breach/potential breach regarding your mobile device number.

Consent Form SMS/Text Addendum Signature

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for receiving text message medication reminders for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary in this text messaging service and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the study team and third-party vendor to have access to my mobile device number.	
4. I agree to take part in the mobile device text message reminder for the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

APPENDIX F: WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers

requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where

consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development Barbara L. Powers Digitally signed by Barbara L. Powers, MSN, PhD DN: cn=Barbara L. Powers, MSN, PhD, o=Clear Creek Bio, Inc., ou=Clinical Operations, email=bpowers@clearcreekbio.com, c=US Date: 2018.10.13 13:32:46 -04'00'	Date: 13 OCT 2018
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Chemistry and Manufacturing/Quality David P. Hesson, PhD Digitally signed by David P. Hesson, PhD Date: 2018.10.13 14:46:26 -04'00'	Date: 13 OCT 2018
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Revision History/Amendments:

Version Number	Date
1.0	31 May 2018
2.0	04 June 2018
3.0	04 October 2018
4.0	11 October 2018

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)

Study No: CCB-01

Version Date: 11 October 2018

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IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal Dose(10%, 50%, 90%)
LPS	Lipopolysaccharide
M	Molar
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar

Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	● To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. ● To characterize the pharmacokinetic (PK) profile of brequinar. ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. ● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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. Subject dosing will be adjusted based on safety/tolerability and DHO level. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each may be added if the Cohort 1 starting dose requires adjustment. Cohorts 2 and 3 may be expanded to 6 subjects using a 3 + 3 design if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the starting dose-adjustment part of the study, an expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated dose from Cohorts 1 – 3. Safety and tolerability will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs, bone marrow sampling, and adverse event reporting. Bone marrow sampling (bone marrow aspirate and core biopsy) will also be utilized for efficacy. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	• Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	• Rates of treatment-emergent adverse events. • Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. • Event free survival (EFS). • Duration of response. • PK profile of brequinar. • DHO plasma profile.
Exploratory endpoints:	• 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.
Sample Size:	Up to 27 subjects

Number of Sites:	3 – 5
Study Period:	An enrollment period of 18 - 24 months is expected.

Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial.
	2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification who have exhausted available therapy.
	3. ECOG Performance Status 0 to 2.
	4. Cardiac ejection fraction ≥ 40%
	5. Adequate hepatic function (unless deemed to be related to underlying leukemia).
	    1. Direct bilirubin ≤ 2 x ULN
	    2. ALT ≤ 3 x ULN
	    3. AST ≤ 3 x ULN
	6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
	7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
	8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
	9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to meet this criterion). 3. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 4. Pre-existing liver disease. 5. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 6. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 7. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome. 8. AML relapse less than 6 months following stem cell transplantation. 9. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 10. Active cerebrospinal involvement of AML. 11. Diagnosis of acute promyelocytic leukemia (APL) 12. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 13. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 14. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage,

	hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 15. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.
Treatment	Subjects will self-administer oral brequinar twice weekly (every 84 hours +/- 6 hours). Treatment cycles will be 2 weeks. Visits will take place at least every 2 weeks through 3 months; visits thereafter will be every 2 – 4 weeks at the discretion of the investigator at each site. Inter-cohort and intra-subject dose adjustments may occur throughout the study as outlined in the sections below. Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: - Demographics (height, weight, date of birth, gender, race, ethnicity) - Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) - Concomitant medications. - Physical examination (including weight). - Vital signs (heart rate, respiratory rate, blood pressure, body temperature). - Pregnancy test for women of childbearing potential (WOCBP) - ECOG performance assessment. - Hematology/chemistry. - 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function. - Bone marrow sampling - Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. **Cycle 1 Day 1:** - Collect any adverse events or new concomitant medications since Screening. - Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.

	– Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP and 12-lead ECG. – Review results and confirm subject remains eligible for the study. – Determine subject's starting dose based on the respective cohort mg/m^2 starting dose. – Dispense study medication. – Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. – Enroll subject for text message reminders if the subject consents to that service. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 2**: – Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 3**: – Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 4**: – Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. **Cycle 1 Day 8**: – Vital signs. – Check the diary/elicit information about AEs/new concomitant medications since the last visit.

	- Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication. - Process and store brequinar/DHO samples per the supplied laboratory manual. - Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8). **<u>Cycle 2 (and any Dose Adjustment Cycle)</u>** Repeat this visit as needed whenever any dose adjustment is required. **Day 1:** - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Take vital signs and perform physical examination (including weight). - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples. - Process and store brequinar/DHO samples per the supplied laboratory manual. - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below. - If dosing will continue, dispense study medication. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) **Day 8:** - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Vital signs. - Collect pre-dose brequinar/DHO and hematology/chemistry samples. - Perform bone marrow sampling for flow cytometry (window ±7 days). - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose. - Process and store brequinar/DHO samples per the supplied laboratory manual. - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume,

	determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose. - Continue to withhold study drug if safety remains unacceptable. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8). Subjects may undergo dose adjustments at any time using the guidelines presented in Section 7 of the protocol. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2, with the exception of Cohort 1 subjects who may not escalate above the 500 mg/m^2 starting dose. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects. Dose adjustments are permitted throughout the study (except for the restriction of no escalation in Cohort 1) for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. **<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)** Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle. In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow aspiration as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks (visit interval at the investigator's discretion). A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response (Figure 1). **Day 1:** - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Collect pre-dose brequinar/DHO and hematology/chemistry samples. - Conduct physical examination, vital signs, urine pregnancy test for WOCBP 12-lead ECG and bone marrow sampling (note that bone marrow is collected on study Day 22 (C2D8 ± 7 days), at Day 43, and

	then every 12 weeks; the Day 43 sample will be assessed for hematological toxicity). - Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety). - Dispense study medication. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples. **Final Visit** This visit is to take place when a subject is discontinuing from the study. - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Collect brequinar/DHO and hematology/chemistry samples. - Collect unused study medication. - Conduct physical examination, vital signs, urine pregnancy test for WOCBP (if ≥4 weeks since previous), 12-lead ECG (if ≥4 weeks since previous), and bone marrow sampling (if > 12 weeks since previous bone marrow sample obtained). - Review the safety information and determine whether the subject has acceptable safety or unacceptable safety. - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples. - Stop text message reminders. **Follow Up Visit (2 weeks after Final Visit)** - Contact subject to elicit information about AEs/new concomitant medications since the last visit. Survival information will be collected while the study is ongoing. **Unscheduled Visits** Unscheduled visits and tests to assess AEs are permitted as needed.

Safety/ Tolerability

Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.

Exceptions to Grade 3 Nonhematologic AEs

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.
Fatigue	Grade 3 fatigue lasting less than 1 week.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.

For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

Safety/Tolerability – Cohort Level

Acceptable safety/tolerability at the cohort level is defined below:

	a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose. b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. Upon cohort expansion to 6 subjects, if a total of ≤2 out of 6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
Cohort Starting Doses	Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety. After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1. As noted above, additional subjects may be added to each of these cohorts if safety needs to be further explored. If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit. See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.
Expansion Cohort	Once a dose has been reached that has adequate DHO level and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions about adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects may also undergo individual dose adjustment. See Section 7.3.3 for the expansion cohort safety rules.
Individual Dose Adjustment Guidelines	With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a

maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be escalated, maintained (stable dose), held then reduced, or discontinued. The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned.

As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO level (with the exception of no escalation for Cohort 1 subjects). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels and bone marrow results have been reviewed.

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

The intrasubject dose-adjustment criteria are presented below.

Intra-subject Dose Adjustment Criteria*

Acceptable Safety/Tolerability? (see safety definition above)	**Adequate DHO Level?**	**Planned Intra-Subject Dose Adjustment**
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue

	<table><tr><td></td><td></td><td>further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.</td></tr><tr><td colspan="3">*Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.</td></tr></table>
Brequinar/DHO	Plasma brequinar/DHO samples are to be obtained for each subject for the first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to subjects in the expansion cohort who will have trough sampling only prior to the start of each two-week cycle. A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3. The 84-hour post dose brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP. Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system

	organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

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2 INTRODUCTION

2.1 Background: Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10%.[1] It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

2.2 Dihydroorotate dehydrogenase (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous enzyme, and lack of its level is not compatible with life. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

2.3 Brequinar

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity

against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

2.4 Rationale for the Planned Trial

This study is designed to obtain safety and efficacy data for brequinar in patients with AML.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in more detail in Section 7.5.

2.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-a-week

administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a biweekly schedule of brequinar dosed approximately every 84 hours, while measuring plasma DHO to fine-tune the dosing schedule that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see Brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggest that a starting dose for Cohort 1 of 500 mg/m^2 p.o. will be safe and well-tolerated in subjects with AML. Each subject's subsequent dosing may be adjusted depending on the safety, tolerability and DHO level obtained during the period following dose adjustment. Each of the two planned subsequent cohorts may also have an adjusted starting dose, again depending on safety, tolerability and DHO level observed in previous cohorts. See Section 7.4.

2.5 Risk/Benefit of Brequinar

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of AML is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment in patients with AML is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with AML typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

2.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the guidelines presented in Section 9.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and

treatment are described in Sections 9.10 and 9.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 9.7.

2.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

2.7.1 CYP Interactions

No formal drug-drug interaction studies have been performed with medications commonly used in treating AML. The nonclinical studies have demonstrated there is no first-pass metabolism, and there have been no apparent hepatotoxic effects in the clinical studies performed to date.

2.8 Steps to be Taken to Control or Mitigate Risks

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 9.

3 TRIAL OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML.

3.2 Secondary Objectives

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

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

4 TRIAL DESIGN

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 may be adjusted based on safety/tolerability and DHO level.

Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting doses. Cohorts 2 and 3 may be expanded to 6 subjects if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the cohort dose-adjustment part of the study, an expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized for efficacy. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in more detail in Section 7.

5 TRIAL ENDPOINTS

5.1 Primary Endpoint

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

5.2 Secondary Endpoints

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

5.3 Exploratory Endpoints

- 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

6 TRIAL POPULATION

6.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

6.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial.
2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification who have exhausted available therapy.
3. ECOG Performance Status 0 to 2.
4. Cardiac ejection fraction $\geq 40\%$
5. Adequate hepatic function (unless deemed to be related to underlying leukemia)
    a. Direct bilirubin ≤ 2 x ULN
    b. ALT ≤ 3 x ULN
    c. AST ≤ 3 x ULN
6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of study initiation will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

6.3 Exclusion Criteria

1. Patients in need of immediate leukapheresis are excluded.
2. White blood count > 25 x 10^9/L (note: hydroxyurea is permitted to meet this criterion).

3. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.
4. Pre-existing liver disease.
5. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.
6. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:
    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.
    b. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.
7. AML relapse less than 6 months following stem cell transplantation.
8. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).
9. Active cerebrospinal involvement of AML.
10. Diagnosis of acute promyelocytic leukemia (APL).
11. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.
12. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.
13. Prior malignancy, unless it has not been active or has remained stable for at least 3 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
14. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

6.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

7 STUDY TREATMENTS

Subjects will self-administer oral brequinar twice weekly (approximately every 84 hours). Treatment cycles will be 2 weeks. Dose adjustment is to occur as outlined below. Visits will take place at least every 2 weeks through 3 months. More frequent visits are permitted to assess and/or treat adverse events. Less frequent visits (up to 4-week intervals) are permitted after 3 months depending on subject safety/tolerability and response. Cohort 1 will begin at 500 mg/m^2 twice weekly. Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose, but the intra-subject dose may be reduced if unacceptable safety occurs. Subsequent cohorts will have a starting dose that may be adjusted based on the safety/tolerability (Section 7.3.1, Section 7.3.2) and DHO levels of the previous cohort. The dosing for individual subjects may be adjusted based on the safety/tolerability and DHO levels as shown in Section 7.5.

7.1 Description of Brequinar:

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis based on the starting dose of a subject's cohort and the tolerability, safety and DHO level assessed following each dose. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 8 hours after the missed dose. If more than 8 hours have elapsed or if the dose was vomited or if the subject for any reason is unable to take the scheduled dose within 8 hours, omit that dose, and the subject should resume treatment with the next scheduled dose. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

7.2 Treatment Administration

Subjects will take oral brequinar twice weekly (approximately every 3.5 days) e.g., Monday morning and Thursday evening. Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar brequinar/DHO samples. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

7.3 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). After completion of Cohort 1 (which will have a fixed starting dose of 500 mg/m^2 with no dose escalation permitted), safety/tolerability will be used to determine both cohort starting doses for subsequent cohorts and individual dosing adjustments. Safety at the subject level is defined in Section 7.3.1; hematologic toxicity is defined in Section 7.3.1.1; and safety at the cohort level is defined in Section 7.4.

7.3.1 Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting

during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in Table 1.

Table 1. Exceptions to Grade 3 Nonhematologic AEs

Condition	Exception Description
Nausea/ Emesis	Grade 3 nausea and/or emesis resolving 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 ≤ Grade 1 or baseline within 1 week after receiving the maximal supportive therapy based on standard practice.
Fatigue	Grade 3 fatigue lasting less than 1 week.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.

For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

7.3.1.1 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

7.3.2 Safety/Tolerability – Cohort Level

Acceptable safety/tolerability at the cohort level is defined below:

a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. If a total of ≤2 out of

6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.

7.3.3 Safety/Tolerability – Expansion Cohort

The safety and tolerability of the starting dose for the Expansion Cohort will have been determined during the Cohort Level adjustments defined in the preceding section. If >1 of the first 5 subjects in the Expansion Cohort cannot tolerate this starting dose based on the rules for safety and tolerability at the subject level (Section 7.3.1), the starting dose for the next 5 subjects in this cohort will be reduced by 75 mg/m^2. If >1 of the second 5 subjects cannot tolerate the reduced starting dose, the starting dose will be again reduced by 75 mg/m^2 for the final 5 subjects planned for this cohort. All of these subjects are eligible for intra-subject dose adjustment and will follow the same individual subject safety rules for either stopping dosing or dose adjustment as presented in Section 7.3.1 and Section 7.5.

7.4 Cohort Starting Doses

Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety.

After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1. As noted in Section 7.3.2, additional subjects may be added to Cohorts 2 and 3 to further explore safety, if needed.

If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit.

See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.

7.5 Individual Dose Adjustment Guidelines

With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be adjusted from the starting dose by being escalated, maintained (stable dose), held then reduced, or discontinued (except in Cohort 1 where subjects' doses may not be escalated beyond the 500 mg/m^2 starting dose). The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned. As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing

unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO levels (except in Cohort 1). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels, and bone marrow results have been reviewed.

7.5.1 DHO Threshold

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

Table 2 and Figure 1 present the intra-subject dose-adjustment criteria. Note that there is no dose escalation in Cohort 1.

Table 2. Intra-Subject Dose Adjustment*

Acceptable Safety/Tolerability? (see safety definition above)	Adequate DHO Level?	Planned Intra-Subject Dose Adjustment
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.

* Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.

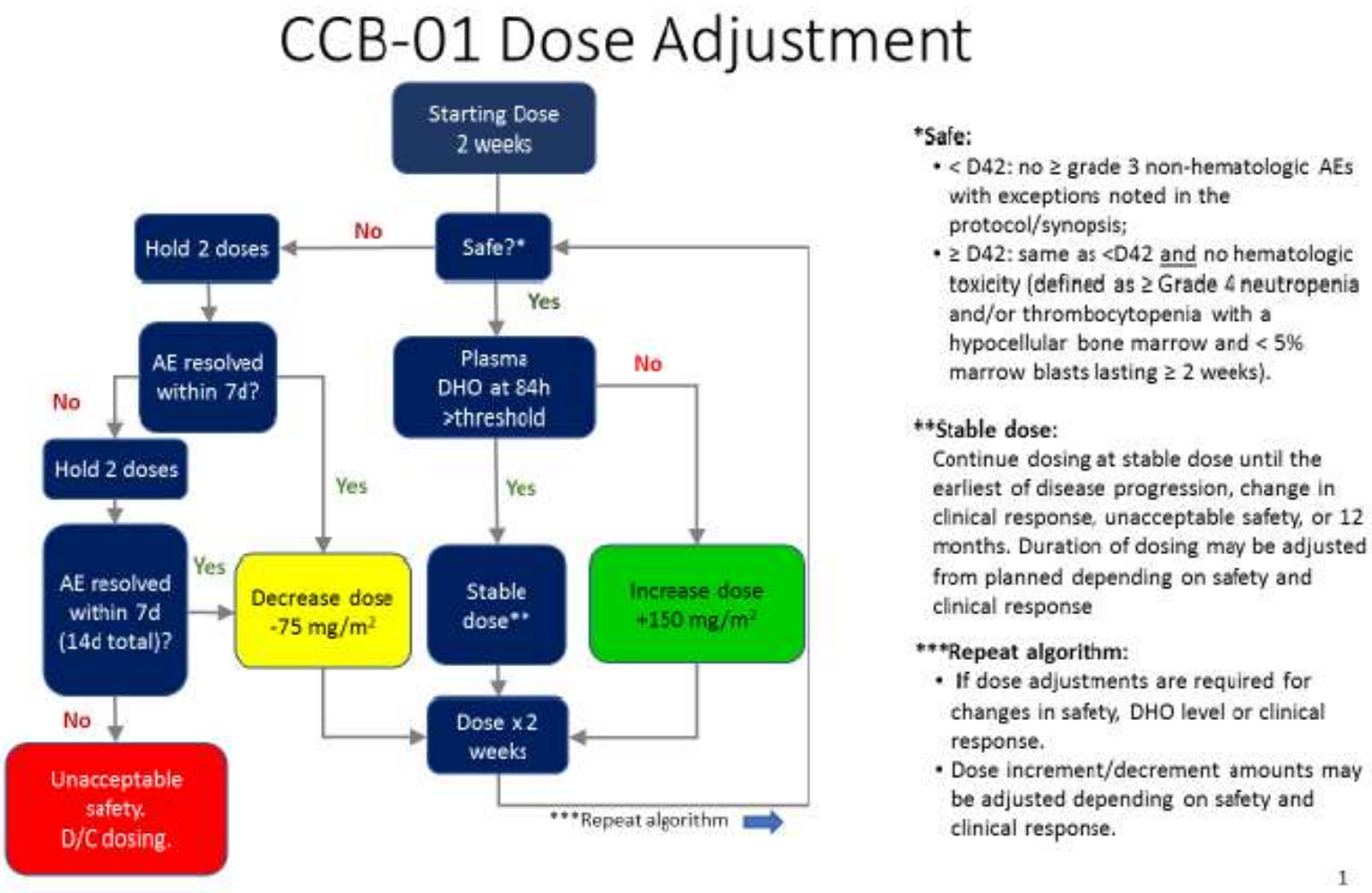

Figure 1. Dose Adjustment – Subject Level

7.6 Medication/AE Diary

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

7.7 Bone Marrow Biopsy

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the C2D8 visit ± 7 days, and one at Day 43 ± 7 days; thereafter, bone marrow sampling will be every 12 weeks and at the Final Visit. If a participant develops frank evidence of progression of AML during the course of treatment based on laboratory or clinical assessment, then he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at the Day 43 visit, then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for the Day 43 visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

7.8 Flow Cytometry

Peripheral blood samples are to be obtained for flow cytometry in Cycle 1 at baseline (Day 1 pre-dose), Day 2, and Day 3

7.9 Expansion Cohort

Once a dose has been reached that has adequate DHO level (as mentioned above, “adequate” trough DHO may be adjusted after reviewing DHO level, safety and clinical response data), and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions regarding adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects are eligible for intra-subject dose adjustment (see Section 7.3.1 and Section 7.5).

The expansion cohort will follow the same visit procedures as the Maintenance Dose cohort and visit frequency may vary from 2 to 4 weeks.

7.10 Study Drug Discontinuation

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh), the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued if there is evidence of unacceptable safety/tolerability that does not resolve within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 30 days after the last dose of brequinar or until they receive another treatment for their AML. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

7.11 Brequinar Pharmacokinetics (PK) / Dihydroorotate (DHO) Plasma Levels

Plasma samples for brequinar/DHO levels are to be obtained for each subject for the subject's first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is baseline at 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to Cycle 1 for subjects in the expansion cohort, see below.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84h}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.

Directions regarding sample processing are presented in a separate laboratory manual.

7.12 Concomitant Medication/Treatment

The name, start date (if known), indication for use and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;
- Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.

7.12.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

7.13 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

7.14 Storage, Stability, Labeling and Packaging

7.14.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

7.14.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-01

Contents: 100 or 250 mg capsules

For oral use only. Take with approximately 8 ounces water every 3.5 days.

Subject Number: XX-XXXX

Treatment Duration: As directed

IND: 138355 Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

7.14.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution. No randomization codes are necessary for this open-label study.

7.14.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the Investigator's Brochure.

7.14.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the

next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

8 CONDUCT OF THE TRIAL

8.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

8.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

8.3 Institutional Review Board / Ethics Committees

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

8.4 Schedule of Events

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 14.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include: blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium).

Hematology tests include: hemoglobin, hematocrit, complete blood count with differential and platelet count.

In addition to the already scheduled weekly chemistry assessment during Cycles 1 and 2 for each subject, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.

8.5 Study Conduct

8.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity).
- Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

8.5.2 Cycle 1

Cycle 1 Day 1:

- Collect any adverse events or new concomitant medications since Screening.
- Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP, and 12-lead ECG.
- Review results and confirm subject remains eligible for the study.
- Determine subject's starting dose based on the respective cohort mg/m^2 starting dose.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- Enroll subject for text message reminders if the subject consents to that service.

- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual

Cycle 1 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 4:

- Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.

Cycle 1 Day 8:

- Vital signs.
- Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8).

8.5.3 Cycle 2 (and any Dose Adjustment Cycle)

Repeat this visit as needed when dose adjustment is ongoing.

- Day 1:
  - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Take vital signs and perform physical examination (including weight).
  - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below.
  - If dosing will continue, dispense study medication.
  - Dispense calendar/diary.

- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)

- Day 8:
  - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Vital signs.
  - Collect pre-dose brequinar/DHO and hematology/chemistry samples.
  - Perform bone marrow sampling (window ±7 days).
  - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose.
  - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Continue to withhold study drug if safety remains unacceptable.
  - Dispense calendar/diary.
  - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
  - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8).

Subjects may undergo dose adjustments at any time using the guidelines presented above. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects.

Dose adjustments are permitted throughout the study for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. This upper limit may be adjusted depending on safety/tolerability/DHO/brequinar PK or other factors during the study.

8.5.4 Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle.

In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow sampling as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks per the investigator's discretion.

A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response.

Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO and hematology/chemistry samples.
- Conduct physical examination vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (note that bone marrow is collected at the C2D8 visit (window ±7 days), at Day 43, then every 12 weeks; the Day 43 sample will be assessed for hematological toxicity).
- Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety).
- Dispense study medication.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.

8.5.5 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (do not collect bone marrow if < 4 weeks since previous bone marrow sample obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

8.5.6 Follow Up Visit (2 weeks after Final Visit)

- Contact subject to elicit information about AEs/new concomitant medications since the last visit. Survival information will be collected while the study is ongoing.

8.5.7 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within four (4) weeks after the final dose.

8.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified window, it will not be necessary to file a protocol violation.

8.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

8.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

8.9 Short Messaging Service (SMS) Medication Reminders

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted in part to protect the security and privacy of protected health information (PHI). Covered entities (e.g., health care providers engaged in certain electronic transactions, health plans, and health care clearinghouses) that create, maintain, transmit, use, and disclose an individual's PHI are required to meet HIPAA requirements.

HIPAA's Privacy Rule restricts uses and disclosures of PHI, creates individual rights with respect to their PHI, and mandates administrative requirements. Among other requirements, the privacy rule requires a covered entity to reasonably safeguard PHI from any intentional or unintentional use or disclosure that is in violation of the requirements of HIPAA.

HIPAA's Security Rule requires covered entities to ensure confidentiality, integrity, and availability of its electronic PHI, to protect against reasonably anticipated threats or hazards to the security or integrity of its electronic PHI, to protect against reasonably anticipated impermissible uses and disclosure of its electronic PHI, and to ensure compliance by their workforce. Additionally, the Security Rule requires covered entities to put in place detailed administrative, physical, and technical safeguards to protect electronic PHI. To do this, covered entities are required to implement access controls and set up backup and audit controls for electronic PHI in a manner commensurate with the associated risk.

For protocol CCB-01, the Sponsor intends to utilize a third-party vendor with a HIPAA-compliant platform to send one-way text message reminders to study participants who have a mobile device. The SMS/text message will be sent on the days and times he or she is to take his or her study medication, e.g., Monday mornings and Thursday evenings. The exact timings of the reminders will be customized for each study participant. The PHI the third-party vendor receives will be restricted to the participant's mobile device number and study identification number. The study participant is not to reply to the text message except to "opt out" from the service by sending "STOP" in the message body. In any other case if he/she sends a text message, the texting service will reply with a message indicating that messages sent by participants are not being monitored. Study participants must agree to "opt in" for this service and can "opt out" at any time even if they initially agreed. Study participants will need to sign an addendum to the informed consent document documenting their decision prior to enrollment in the system (see Appendix 14.5).

The third-party vendor will sign an agreement with the Sponsor to use participant data only for the purposes of this study. Data will be purged from the vendor's servers at the conclusion of the trial upon written request by the Sponsor. Data will remain in the vendor's encrypted back-up files that will be maintained per HIPAA-compliant standards.

9 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs. Disease progression should not be reported as an AE unless worsening of signs and symptoms occur, or death from disease progression.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. If

the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.0* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

9.1 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

9.2 Classification of Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

9.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition ;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following a SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox@novellaclinical.com

MEDICAL MONITOR: **Robert Sims, MD**
E-mail: robert.sims@novellaclinical.com;
YYA36071medmon@novellaclinical.com
Telephone: 614-721-2630
24-hour safety line: 1-866-758-2798 or 919-313-7111
Fax: 206-826-0483

Sponsor Representative: **Barbara Powers, MSN, Ph.D.**
E-mail: bpowers@clearcreekbio.com
Telephone: 484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

9.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

9.5 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring

of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

9.6 Hematologic Adverse Events

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's

life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

9.7 Management of Myelosuppression

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

9.8 Differentiation Syndrome

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
  - Control of leukocytosis with hydroxyurea;
  - Prompt administration of corticosteroids at a suggested dose of 10 mg of

dexamethasone IV every 12 hours until disappearance of symptoms and signs, continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated without dose reduction once the participant's clinical condition improves, upon discussion with the Sponsor.

9.9 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC $< 25 \times 10^9$ /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100×10^9 /L or WBC $< 25 \times 10^9$ /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100×10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).
- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 2 provides a flow chart for TLS monitoring.

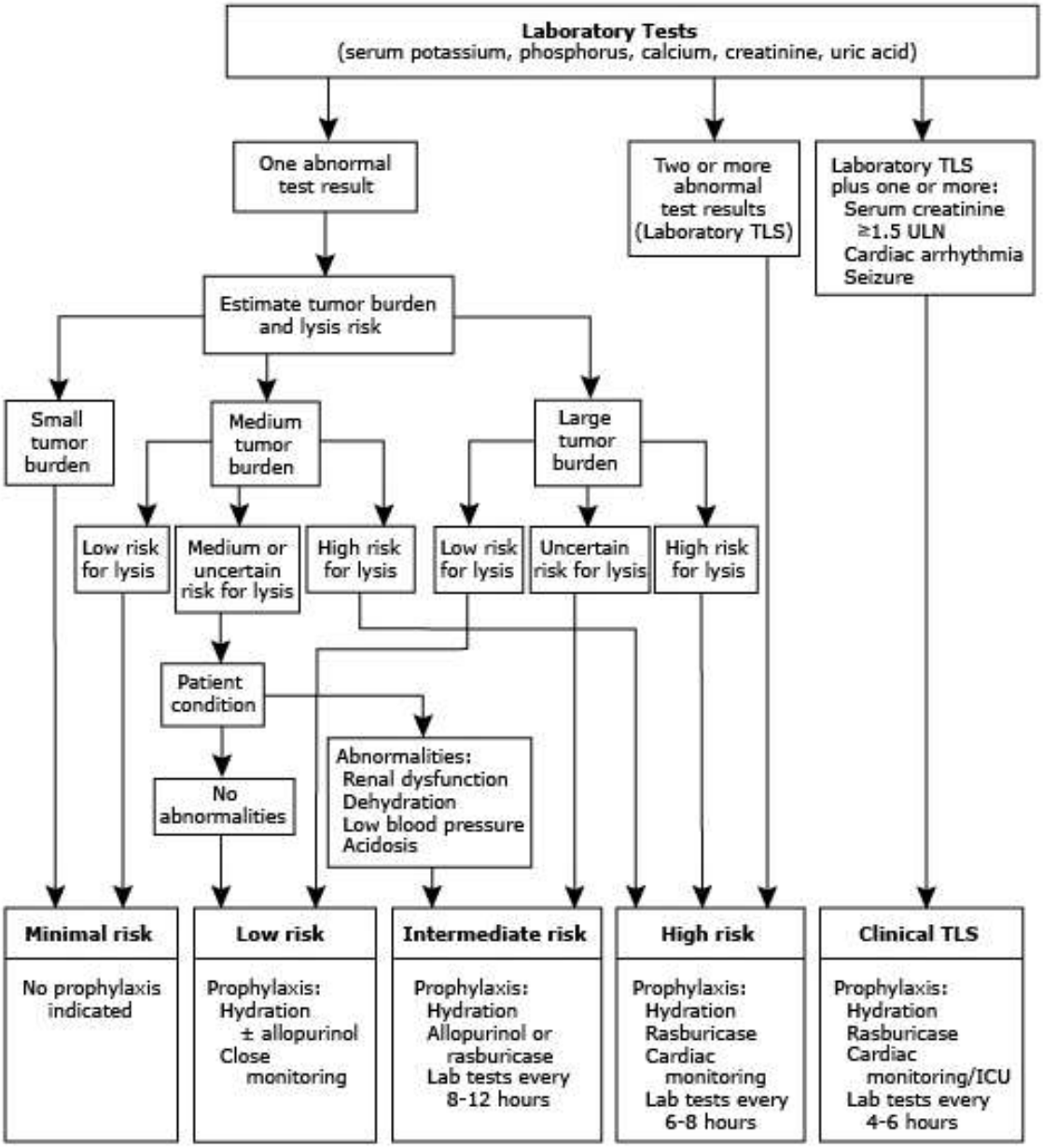

Figure 2. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

9.10 Infection Prophylaxis

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

9.11 Growth Factor Support

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

9.12 Management of Nausea, Vomiting, and Diarrhea

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

10 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

10.1 Study Populations for Analysis

The analysis sets are defined in Table 3.

Table 3. Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

10.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

10.3 Efficacy Analyses

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 4 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 4. Efficacy Analyses

Endpoint	**Statistical Analysis Methods**
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event

	endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

10.4 Other Endpoints

Brequinar Pharmacokinetics (PK)

Blood samples for PK analysis will be obtained at pre-specified times. Plasma PK parameters of brequinar including steady-state plasma concentration (Css); elimination half-life ($T_{1/2}$); Area under the concentration curve (AUC); systemic clearance (CL) and volume of distribution at steady state (Vss) will be estimated by compartmental and non-compartmental analysis (WinNonlin or similar).

Concentration data and PK parameters will be tabulated and summarized using descriptive

statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Blood samples for DHO analysis will be obtained at pre-specified times and will be summarized. Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

10.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting dose. The cohorts with 3 subjects may be expanded to 6 subjects depending on safety outcomes within the cohort. An expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3.

10.6 Randomization

No randomization scheme is needed for this open label study.

10.7 Pooling of Study Centers

Not applicable to this small, early phase study.

10.8 Interim Analysis

No interim analysis is planned for this trial.

11 INVESTIGATOR RESPONSIBILITIES

11.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 14.6) to indicate commitment to comply with the contents.

11.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 11.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

11.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

11.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

11.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or

of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

11.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

11.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

12 SPONSOR RESPONSIBILITIES

12.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

12.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

12.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

12.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

12.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

12.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

13 REFERENCES

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4. Sykes DB, Kfoury YS, Mercier FE, et al. Inhibition of dihydroorotate dehydrogenase overcomes differentiation blockade in acute myeloid leukemia. Cell 2016; 167(1): 171-186.
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14 APPENDICES

14.1 APPENDIX A: CCB-01 Schedule of Events

CCB-01 Schedule of Events	**Screen[b]**	**Cycle 1 (Study Days 1 – 14)**					**Dose Adjustment Cycle (Cycle 2 and beyond as needed)**		**Maintenance Dose Cycle (no dose adjustment) Every 2 weeks**	**Final Visit**	**F/U Phone Call**	**Survival**
Procedures[a]		**D1**	**D2**	**D3**	**D4**	**D8**	**D1**	**D8**	**D1**		**Final Visit + 2 wks**	
Informed Consent[b]	X											
AE/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Medical history[c]	X											
Demographics[d]	X											
Physical Exam[d]	X	X					X		X	X		
Vital Signs[d]	X	X				X	X	X	X	X		
Pregnancy Test[e]	X								X	X		
ECOG Performance Status	X											
Hematology/Chemistry[f]	X	X				X	X	X	X	X		
Flow Cytometry[g]			X	X								
Chromosomal/mutational testing[h]	X											
12-lead ECG	X								X	X		
MUGA/Echocardiogram	X											
Bone Marrow Sampling[i]	X							X		X		
Brequinar/DHO Plasma Sample[j]		X	X	X	X	X	X	X	X	X		
Biobanking samples[k]	X								X	X		
Ship DHO Plasma Samples						X		X	X			
Dispense/Collect Study Medication		X					X		X	X		
Dispense/Collect Subject Calendar/Diary		X					X		X	X		
Survival Assessment												X

a. Visit window of ± 1 day for dose escalation cycles; window of ± 3 days for non dose escalation cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <72h since Screening assessment.
c. Medical history is to include AML diagnosis, previous AML treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Physical exam is to include weight.
e. For women of childbearing potential only.
f. In addition to the already scheduled weekly chemistry assessment during Cycles 1 and 2 for each subject, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.
g. Flow cytometry testing of peripheral blood is to be obtained at 0 (pre-dose C1D1), post dose 48 and 72 hours.
h. Testing panel is per institutional standard of care; obtain sample at Screening.
i. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking further analysis. Perform bone marrow sampling at screening, at study Day 22 (C2D8), at Day 43, and once every 12 weeks after a stable dose has been reachedTiming of this procedure may be adjusted to ensure results are available for the next clinic visit.
j. Brequinar/DHO plasma sampling schedule: Cycle 1: 0 (pre-dose), post dose 1, 2, 4, 6, 24, 48, 72 hours and C1D8 pre-dose (+84h after C1D4 dose); Cycle 2 and adjustment cycles: pre-dose Days 1 and 8; every 2-week Maintenance Cycle until 3-months on drug: pre-dose Day 1 and every 2 to 4 week Maintenance Dose Cycle beyond 3-months on drug. Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Cycle 2 and beyond plasma brequinar/DHO draws ±4h. Ensure trough samples (e.g., C1D1, C2D1, C3D1) are obtained prior to dosing. Plasma samples for brequinar/DHO for expansion cohort are to be obtained prior to dosing on Day 1 of each 2-week cycle for the first 3 cycles, then every 12 weeks.
k. Biobanking samples (bone marrow) are to be collected whenever bone marrow sampling is performed.

14.2 APPENDIX B: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14.3 APPENDIX C: Brequinar/DHO Plasma Sampling

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Brequinar and DHO plasma samples are to be obtained at the following time points (±30 minutes through 6h, then ±2h for the 24h, 48h, 72h and 84h samples:

	Cycle 1									Cycle 2*		Maintenance Dose Cycle	Final Visit
	D1					D2	D 3	D 4	D8	D1	D8	D1	
Time Point	Pre-dose	1h	2h	4h	6h	24h	48h	72h	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose

*Or any cycle where the brequinar dose has been adjusted from the previous 2-week dose.

14.4 APPENDIX D: Common Terminology Criteria for Adverse Events (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

14.5 APPENDIX E: Sample Subject Consent Form

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 2.0 04June2018>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will take the study medication about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF and MUGA scan or echocardiogram to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

Cycle 1 Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.

- Have a physical examination (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and still choose to participate, you will be given adequate study medication for 2 weeks (4 doses).
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Cycle 1 Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit. You will take your second dose of study medication this evening.
- **Cycle 1 Day 8**:

At this visit, you will:

- Have your vital signs checked.
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Take your next dose of study medication in the clinic.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.

Cycle 2

You will return to the clinic 2 weeks after starting the study medication. The study team may adjust your dose of study medication (you may be given more or less of the drug) depending on your safety results, laboratory, and DHO levels. This visit may be repeated as needed if your dose adjustment continues.

- **Day 1**:
  - Your unused study medication will be collected (if you have any), and your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
  - Your vital signs will be checked and a physical examination performed.

- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given adequate medication for another 2 weeks (4 doses). Take your next dose of study medication in the clinic.

- **Day 8:**

At this visit, you will:

- Have your vital signs checked.
- Have a bone marrow sample taken for flow cytometry (window ±7 days).
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will continue to take the medication dispensed to you.

Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once you have reached a "stable dose" where no more dose adjustments seem to be needed, you will return to the clinic every 2 weeks and have the procedures below. After you've been taking the study medication for 3 months, your study doctor may space your visits out to every 4 weeks.

Day 1:

At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for pre-dose brequinar/DHO and hematology/chemistry.
- Have a physical examination, vital signs, urine pregnancy test for women able to bear children, 12-lead ECG.
- Have a bone marrow sampling (the bone marrow aspiration sampling is performed at study Day 22 ±7 days, at study Day 43 and repeated every 12 weeks or more often if there is a safety concern).
- Your study team will review the laboratory results/safety information and determine whether you should stay at the same dose or whether you should temporarily stop taking the study medication or whether the dose should be changed.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given additional medication and continue to take the medication dispensed to you as directed by the study team.
- Your diary/calendar will be collected and a new one provided to you.

Final Visit

This visit is to take place if you or your study team decide you should stop participation in the study or you have reached 12 months of study participation. At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for brequinar/DHO, flow cytometry and hematology/chemistry.
- Have a physical examination (including weight), vital signs, urine pregnancy test for women able to bear children, 12-lead ECG and bone marrow sampling (unless it has been less than 4 weeks since the previous bone marrow sampling).
- Turn in any unused study medication.
- Turn in your calendar/diary.

Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by phone to be asked about any new medical events or new or changed medications since your last clinic visit.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea
- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either

stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.
- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.
- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.
- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.
- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to

the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

Addendum to Informed Consent for Short Messaging Service (SMS/text)

Reminders for Protocol CCB-01

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Addendum ICF Version 1.0 31May2018>

WHY AM I BEING ASKED TO SIGN THIS ADDENDUM TO THE CONSENT?

You are being asked to sign this addendum to the consent because you have agreed to participant in study CCB-01 and because it is very important for you to take your study medication at the correct times (e.g., Monday mornings and Thursdays evenings). One effective way to help you remember to take your medication on time is for you to receive a text reminder on your phone. The sponsor of the study (Clear Creek Bio, Inc.) is using an external vendor to generate a text message reminder that will be sent to your mobile device when it is time for you to take your study medication.

VOLUNTARY NATURE OF THIS SERVICE

It is entirely optional for you to receive this service. Your decision to receive text message reminders for your medications will not in any way affect your ability to enroll in the study. You may also "opt out" at any time by responding "STOP" to the messages, or by contacting your study team.

DESCRIPTION OF THE NATURE OF THE DATA YOU WILL PROVIDE
You will provide your mobile device number to the study team who will then enter the number into the third-party vendor's system for sending out the text reminders.

DESCRIPTION OF HOW THE DATA WILL BE USED
The only information that will be shared with the third-party vendor is your mobile device number and your study participant identification number. The system is set up so that one-way messages are sent from the service to you. You should not reply to the messages you receive except to "opt out". If you do send a message, the texting service will reply with a message indicating that the messages you may send are not being monitored.

WHAT WILL THE MESSAGE SAY?
On the twice-weekly schedule (i.e., Monday mornings and Thursday evenings), you will receive a text with the following information: “It is time for you to take your CCB-01 study medication. Thank you for participating in this study.” You may delete this message after reading.

DESCRIPTION OF HOW THIS DATA WILL BE SECURELY MANAGED
The mobile device number you provide to be used for these reminders will be managed in a manner that ensures the best possible security. The mobile device number will not be shared with any other third-party vendor or the sponsor of this study (Clear Creek Bio, Inc.).

WHAT IF I DON’T HAVE A PHONE THAT CAN RECEIVE TEXT MESSAGES?
If you do not have a mobile phone or cannot receive text messages, you cannot participate in receiving these text message reminders.

DISCLOSURES OF RISKS AND VULNERABILITIES
Although unlikely, it is possible that the unencrypted text messages you receive could inadvertently be seen by someone else. Because the messages are de-identified (your name will not appear), the most information that could be seen would be that you are participating in a study. You are not sending any information back to the third-party vendor, so nothing you send could be seen by mistake.

The study team members are not responsible for any loss or breach of data that results from something beyond their control, e.g., you lose your mobile device containing text messages reminders, or a third-party vendor or host experiences a server/data breach.

Standard text/data messaging rates apply to these messages, and because some mobile phone providers charge an additional fee for the sending and receiving of text messages, you might be charged additionally by your mobile phone provider if you choose to receive the text message reminders.

PROCESS FOR NOTIFYING PARTICIPANT IN CASE OF AN ACTUAL OR POTENTIAL SECURITY BREACH

If the third-party vendor that has your mobile device number experiences a breach or a potential breach, the third-party vendor will notify the sponsor of this study, Clear Creek Bio, Inc. The sponsor will notify the study team at each participating institution, and the study team will contact you regarding the possible risks associated with the breach/potential breach regarding your mobile device number.

Consent Form SMS/Text Addendum Signature

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for receiving text message medication reminders for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary in this text messaging service and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the study team and third-party vendor to have access to my mobile device number.	
4. I agree to take part in the mobile device text message reminder for the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

APPENDIX F: WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health

care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat

to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development Barbara L. Powers Digitally signed by Barbara L. Powers, MSN, PhD DN: cn=Barbara L. Powers, MSN, PhD, o=Clear Creek Bio, Inc., ou=Clinical Operations, email=bpowers@clearcreekbio.com, c=US Date: 2018.10.22 12:47:09 -04'00'	Date: 22 OCT 2018
PRINT NAME: Barbara L. Powers, MSN, Ph.D.	

Research & Development David P. Hesson, PhD Digitally signed by David P. Hesson, PhD Date: 2018.10.22 17:18:13 -04'00'	Date: 22 OCT 2018
PRINT NAME: David P. Hesson, Ph.D.	

Chemistry and Manufacturing/Quality David P Hesson, PhD Digitally signed by David P Hesson, PhD Date: 2018.10.22 17:18:40 -04'00'	Date: 22 OCT 2018
PRINT NAME: David P. Hesson, Ph.D.	

Sponsor Representative Vikram Sheel Kumar Digitally signed by Vikram Sheel Kumar DN: cn=Vikram Sheel Kumar, o=Clear Creek Bio Inc., ou, email=kumar@clearcreekbio.com, c=US Date: 2018.10.22 13:01:37 -04'00'	Date: 22 OCT 2018
PRINT NAME: Vikram Sheel Kumar, MD	

Revision History/Amendments:

Version Number	Date
1.0	31 May 2018
2.0	04 June 2018
3.0	04 October 2018
4.0	11 October 2018
5.0	16 October 2018

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)

Study No: CCB-01

Version Date: 16 October 2018

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal Dose(10%, 50%, 90%)
LPS	Lipopolysaccharide
M	Molar
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar

Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	● To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. ● To characterize the pharmacokinetic (PK) profile of brequinar. ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. ● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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. Subject dosing will be adjusted based on safety/tolerability and DHO level. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each may be added if the Cohort 1 starting dose requires adjustment. Cohorts 2 and 3 may be expanded to 6 subjects using a 3 + 3 design if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the starting dose-adjustment part of the study, an expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated dose from Cohorts 1 – 3. Safety and tolerability will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs, and bone marrow sampling, and adverse event reporting. Bone marrow sampling (bone marrow aspirate and core biopsy) will also be utilized for efficacy. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	• Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	• Rates of treatment-emergent adverse events. • Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. • Event free survival (EFS). • Duration of response. • PK profile of brequinar. • DHO plasma profile.
Exploratory endpoints:	• 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
Sample Size:	Up to 27 subjects

Number of Sites:	3 – 5
Study Period:	An enrollment period of 18 - 24 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial. 2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification who have exhausted available therapy. 3. ECOG Performance Status 0 to 2. 4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2. 5. Adequate hepatic function (unless deemed to be related to underlying leukemia). 1. Direct bilirubin ≤ 2 x ULN 2. ALT ≤ 3 x ULN 3. AST ≤ 3 x ULN 6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation. 7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease. 8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration. 9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 4. Pre-existing liver disease. 5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 6. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome. 7. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 8. Active cerebrospinal involvement of AML. 9. Diagnosis of acute promyelocytic leukemia (APL) 10. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 11. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 12. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 13. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

Treatment	Subjects will self-administer oral brequinar twice weekly (every 84 hours +/- 6 hours). Treatment cycles will be 2 weeks. Visits will take place at least every 2 weeks through 3 months; visits thereafter will be every 2 – 4 weeks at the discretion of the investigator at each site. Inter-cohort and intra-subject dose adjustments may occur throughout the study as outlined in the sections below. Subjects in Cohort 1 may not escalate beyond the initial 500 mg/m^2 starting dose.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: - Demographics (height, weight, date of birth, gender, race, ethnicity) - Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) - Concomitant medications. - Physical examination (including weight). - Vital signs (heart rate, respiratory rate, blood pressure, body temperature). - Pregnancy test for women of childbearing potential (WOCBP). - ECOG performance assessment. - Hematology/chemistry. - 12-lead ECG to assess cardiac function. - Bone marrow sampling - Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. **Cycle 1 Day 1:** - Collect any adverse events or new concomitant medications since Screening. - Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. - Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP, and 12-lead ECG (if >4 weeks since previous ECG or pregnancy test or per institutional guidelines). - Review results and confirm subject remains eligible for the study. - Determine subject's starting dose based on the respective cohort mg/m^2 starting dose. - Dispense study medication.

	– Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. – Enroll subject for text message reminders if the subject consents to that service. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 2**: – Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 3**: – Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. – Ship the flow cytometry sample per the supplied laboratory manual. **Cycle 1 Day 4**: – Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Process and store brequinar/DHO samples per the supplied laboratory manual. **Cycle 1 Day 8**: – Vital signs. – Check the diary/elicit information about AEs/new concomitant medications since the last visit. – Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication. – Process and store brequinar/DHO samples per the supplied laboratory manual.

	- Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8). **<u>Cycle 2 (and any Dose Adjustment Cycle)</u>** Repeat this visit as needed whenever any dose adjustment is required. **Day 1:** - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Take vital signs and perform physical examination (including weight). - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples. - Process and store brequinar/DHO samples per the supplied laboratory manual. - Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below. - If dosing will continue, dispense study medication. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted) **Day 8:** - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. - Vital signs. - Collect pre-dose brequinar/DHO and hematology/chemistry samples. - Perform bone marrow sampling (window ±7 days). - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose. - Process and store brequinar/DHO samples per the supplied laboratory manual. - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose. - Continue to withhold study drug if safety remains unacceptable. - Dispense calendar/diary. - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)

	– Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8). Subjects may undergo dose adjustments at any time using the guidelines presented in Section 7 of the protocol. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2, with the exception of Cohort 1 subjects who may not escalate above the 500 mg/m^2 starting dose. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects. Dose adjustments are permitted throughout the study (except for the restriction of no escalation in Cohort 1) for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. **<u>Maintenance Dose Cycle</u> (visit every 2 - 4 weeks)** Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle. In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow aspiration as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks (visit interval at the investigator's discretion). A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response (Figure 1). **Day 1:** – Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. – Collect pre-dose brequinar/DHO and hematology/chemistry samples. – Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (note that bone marrow is collected on study Day 22 (C2D8 ± 7 days), at Day 43, and then every 12 weeks or per institutional guidelines; the Day 43 sample will be assessed for hematological toxicity). – Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety). – Dispense study medication. – Dispense calendar/diary.

<table>
<tr><td></td><td>
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.

Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP, 12-lead ECG and bone marrow sampling (do not collect bone marrow or perform ECG if < 4 weeks since previous bone marrow sample or ECG obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

Follow Up Visit (2 weeks after Final Visit)

- Contact subject to elicit information about AEs/new concomitant medications since the last visit.

Survival information will be collected while the study is ongoing.

Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed.
</td></tr>
<tr><td>Safety/
Tolerability</td><td>
Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting during the first 42 days of dosing. Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.

Exceptions to Grade 3 Nonhematologic AEs

<table>
<tr><th>Condition</th><th>Exception Description</th></tr>
<tr><td>Nausea/
Emesis</td><td>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.</td></tr>
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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 < 2 weeks
Fatigue	Grade 3 with duration < 2 weeks

For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

Safety/Tolerability – Cohort Level

Acceptable safety/tolerability at the cohort level is defined below:

a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. Upon cohort expansion to 6 subjects, if a total of ≤2 out of 6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.

Cohort Starting Doses	Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety. After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1. As noted above, additional subjects may be added to each of these cohorts if safety needs to be further explored. If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit. See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.
Expansion Cohort	Once a dose has been reached that has adequate DHO level and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions about adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects may also undergo individual dose adjustment. See Section 7.3.3 for the expansion cohort safety rules.
Individual Dose Adjustment Guidelines	With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be escalated, maintained (stable dose), held then reduced, or discontinued. The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned. As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred. Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO level (with the exception of no escalation for Cohort 1 subjects). Subjects who discontinue

due to unacceptable safety/tolerability or die prior to Day 42 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels and bone marrow results have been reviewed.

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2).

The intrasubject dose-adjustment criteria are presented below.

Intra-subject Dose Adjustment Criteria*

Acceptable Safety/Tolerability? (see safety definition above)	**Adequate DHO Level?**	**Planned Intra-Subject Dose Adjustment**
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.

*Note that Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.

Brequinar/DHO	Plasma brequinar/DHO samples are to be obtained for each subject for the first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to subjects in the expansion cohort who will have trough sampling only prior to the start of each two-week cycle. A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

	The 84-hour post dose brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP. Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi

	• Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

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2 INTRODUCTION

2.1 Background: Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10%.[1] It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

2.2 Dihydroorotate dehydrogenase (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous, essential enzyme. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

2.3 Brequinar

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity

against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

2.4 Rationale for the Planned Trial

This study is designed to obtain safety and efficacy data for brequinar in patients with AML.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in more detail in Section 7.5.

2.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-a-week

administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a biweekly schedule of brequinar dosed approximately every 84 hours, while measuring plasma DHO to fine-tune the dosing schedule that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see Brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggest that a starting dose for Cohort 1 of 500 mg/m^2 p.o. will be safe and well-tolerated in subjects with AML. Each subject's subsequent dosing may be adjusted depending on the safety, tolerability and DHO level obtained during the period following dose adjustment. Each of the two planned subsequent cohorts may also have an adjusted starting dose, again depending on safety, tolerability and DHO level observed in previous cohorts. See Section 7.4.

2.5 Risk/Benefit of Brequinar

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of AML is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment in patients with AML is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with AML typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

2.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the guidelines presented in Section 9.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and

treatment are described in Sections 9.10 and 9.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 9.7.

2.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

2.7.1 CYP Interactions

No formal drug-drug interaction studies have been performed with medications commonly used in treating AML. The nonclinical studies have demonstrated there is no first-pass metabolism, and there have been no apparent hepatotoxic effects in the clinical studies performed to date.

2.8 Steps to be Taken to Control or Mitigate Risks

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 9.

3 TRIAL OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML.

3.2 Secondary Objectives

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

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

4 TRIAL DESIGN

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 may be adjusted based on safety/tolerability and DHO level.

Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting doses. Cohorts 2 and 3 may be expanded to 6 subjects if required by safety assessments as described in Section 7.3.2. Following completion of enrollment in the cohort dose-adjustment part of the study, an expansion cohort of 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized for efficacy. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in more detail in Section 7.

5 TRIAL ENDPOINTS

5.1 Primary Endpoint

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

5.2 Secondary Endpoints

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

5.3 Exploratory Endpoints

- 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

6 TRIAL POPULATION

6.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

6.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial.
2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification who have exhausted available therapy.
3. ECOG Performance Status 0 to 2.
4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2.
5. Adequate hepatic function (unless deemed to be related to underlying leukemia).
    a. Direct bilirubin ≤ 2 x ULN
    b. ALT ≤ 3 x ULN
    c. AST ≤ 3 x ULN
6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Hydrea is allowed up to 48 hours prior to the first dose for patients with rapidly proliferative disease.
8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

6.3 Exclusion Criteria

1. Patients in need of immediate leukapheresis.
2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.

3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.
4. Pre-existing liver disease.
5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:
    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.
    b. Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.
6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).
7. Active cerebrospinal involvement of AML.
8. Diagnosis of acute promyelocytic leukemia (APL).
9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.
10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.
11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
12. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

6.4 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

7 STUDY TREATMENTS

Subjects will self-administer oral brequinar twice weekly (approximately every 84 hours). Treatment cycles will be 2 weeks. Dose adjustment is to occur as outlined below. Visits will take place at least every 2 weeks through 3 months. More frequent visits are permitted to assess and/or treat adverse events. Less frequent visits (up to 4-week intervals) are permitted after 3 months depending on subject safety/tolerability and response. Cohort 1 will begin at 500 mg/m^2 twice weekly. Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose, but the intra-subject dose may be reduced if unacceptable safety occurs. Subsequent cohorts will have a starting dose that may be adjusted based on the safety/tolerability (Section 7.3.1, Section 7.3.2) and DHO levels of the previous cohort. The dosing for individual subjects may be adjusted based on the safety/tolerability and DHO levels as shown in Section 7.5.

7.1 Description of Brequinar:

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis based on the starting dose of a subject's cohort and the tolerability, safety and DHO level assessed following each dose. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 8 hours after the missed dose. If more than 8 hours have elapsed or if the dose was vomited or if the subject for any reason is unable to take the scheduled dose within 8 hours, omit that dose, and the subject should resume treatment with the next scheduled dose. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

7.2 Treatment Administration

Subjects will take oral brequinar twice weekly (approximately every 3.5 days) e.g., Monday morning and Thursday evening. Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. Each dose will generally consist of multiple capsules; all capsules do not need to be swallowed at once but can be spread over up to 15 minutes as needed. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar brequinar/DHO samples. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

7.3 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). After completion of Cohort 1 (which will have a fixed starting dose of 500 mg/m^2 with no dose escalation permitted), safety/tolerability will be used to determine both individual cohort starting doses for subsequent cohorts and individual dosing adjustments. Safety at the subject level is defined in Section 7.3.1; hematologic toxicity is defined in Section 7.3.1.1; and safety at the cohort level is defined in Section 7.4.

The following adverse events are commonly observed in patients with AML and should be differentiated from possible adverse effects of brequinar:

Fatigue, fever, thrombocytopenia, infection, pallor, shortness of breath, weight loss, night sweats, and anorexia.

Prescriptions can be provided in advance for supportive care for common brequinar-related AEs such as mucositis.

7.3.1 Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in Table 1.

If a dose is held due to safety/tolerability issues, the subject should continue to come to the clinic for scheduled visits and to have scheduled assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Table 1. Exceptions to Grade 3 Nonhematologic AEs

Condition	Exception Description
Nausea/ Emesis	Grade 3 nausea and/or emesis resolving 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 ≤ Grade 1 or baseline within 1 week after receiving the maximal supportive therapy based on standard practice.
Fatigue	Grade 3 fatigue with duration < 2 weeks.
Laboratory abnormalities	Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.
Mucositis	Grade 3 with duration < 2 weeks

For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

7.3.2 Safety/Tolerability – Cohort Level

Acceptable safety/tolerability at the cohort level is defined below:

a) If ≥2 out of 3 subjects at a dose level experience unacceptable safety/tolerability leading to dose reduction or treatment discontinuation (a dose limiting toxicity or DLT), then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.
b) If 1 out of 3 subjects at a dose level experiences a DLT, then 3 additional subjects will be added to the cohort and treated at the same dose that led to the DLT. If a total of ≤2 out of 6 subjects has a DLT at that dose, then this dose is considered a safe/tolerated dose. However, if >2 out of 6 subjects at a dose level experience a DLT, then that dose is considered to have unacceptable safety/tolerability and the previous dose which was safe/tolerated must be considered as the highest safe/tolerated dose.

7.3.3 Safety/Tolerability – Expansion Cohort

The safety and tolerability of the starting dose for the Expansion Cohort will have been determined during the Cohort Level adjustments defined in the preceding section. If >1 of the first 5 subjects in the Expansion Cohort cannot tolerate this starting dose based on the rules for safety and tolerability at the subject level (Section 7.3.1), the starting dose for the next 5 subjects in this cohort will be reduced by 75 mg/m^2. If >1 of the second 5 subjects cannot tolerate the reduced starting dose, the starting dose will be again reduced by 75 mg/m^2 for the final 5 subjects planned for this cohort. All of these subjects are eligible for intra-subject dose adjustment and will follow the same individual subject safety rules for either stopping dosing or dose adjustment as presented in Section 7.3.1 and Section 7.5.

7.4 Cohort Starting Doses

Cohort 1 will treat 6 subjects at 500 mg/m^2 twice weekly. No dose escalation is permitted for Cohort 1 subjects, but the dose may be reduced for an individual subject in this cohort if the subject experiences unacceptable safety.

After all subjects in Cohort 1 have completed a 42-day treatment period, up to two additional cohort(s) of 3 subjects each will be added with the starting doses adjusted (escalated or de-escalated) based on both safety/tolerability and adequacy of DHO level results in Cohort 1. As

noted in Section 7.3.2, additional subjects may be added to Cohorts 2 and 3 to further explore safety, if needed.

If all subjects in a cohort have acceptable safety at a dose level, the next cohort's starting dose may be escalated by 150 mg/m^2. If the safety rules are not met at a cohort's starting dose, the next cohort's starting dose will be reduced to the highest dose found to be safe/tolerated in the previous cohort. The planned upper limit for cohort starting dose is 800 mg/m^2. There is no lower limit.

See the "Intra-subject dose adjustment" section for individual subject dosing adjustment criteria.

7.5 Individual Dose Adjustment Guidelines

With the exception of subjects in Cohort 1 whose dose may not be escalated above the 500 mg/m^2 starting dose, intra-subject dose adjustment will be considered every 2 weeks depending on safety and DHO levels. There is a maximum of 2 dose adjustments for each subject within the first 42 days of initiating treatment. Each subject's dose can be adjusted from the starting dose by being escalated, maintained (stable dose), held then reduced, or discontinued (except in Cohort 1 where subjects' doses may not be escalated beyond the 500 mg/m^2 starting dose). The highest dose planned is 800 mg/m^2, however, this upper limit may be adjusted depending on safety, DHO level, and clinical response. There is no lower limit planned. As noted above, safety will be a key part of determining dose adjustments. Subjects who resume dosing at a lower dose after experiencing unacceptable safety may not undergo later dose escalations beyond the dose where the unacceptable safety occurred.

Each subject will continue dosing twice weekly at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and DHO levels (except in Cohort 1). Subjects who discontinue due to unacceptable safety/tolerability or die prior to Day 43 will not be replaced.

Intra-subject dose adjustment increments and duration of dosing may be revised from planned amounts after each preceding cohort's safety, DHO plasma levels, and bone marrow results have been reviewed.

7.5.1 DHO Threshold

Each subject's baseline DHO sample will be obtained at C1D1 prior to dosing. Dose adjustment decisions based on DHO will be determined by DHO trough level (i.e., DHO level obtained pre-dose D8 of the previous cycle). The initial target for "adequate" trough DHO level will be set at 100 ng/mL. This target may be adjusted during the study depending on safety or efficacy signals observed during the study. As described below, dose adjustments are also determined by the investigator based on safety and whether the dose has reached the planned upper limit (currently planned to be 800 mg/m^2). If the DHO level is not available for any reason, the subject is to continue treatment at the current dose unless there is unacceptable safety.

Table 2 and Figure 1 present the intra-subject dose-adjustment criteria. Note that there is no dose escalation in Cohort 1.

Table 2. Intra-Subject Dose Adjustment*

Acceptable Safety/Tolerability? (see safety definition above)	Adequate DHO Level?	Planned Intra-Subject Dose Adjustment
Yes	Yes	Maintain; continue at same dose.
Yes	No	Escalate by 150 mg/m^2 for the next 2-week cycle up to a maximum of 800 mg/m^2.
No	Regardless of DHO	Hold two doses (one week), then reassess AE; if AE has resolved to ≤ Gr. 2, de-escalate dose by 75 mg/m^2 and resume dosing. If AE has not resolved, reassess again in one week. If AE does not resolve to ≤ Gr. 2 by two weeks after dosing held, discontinue further dosing. Subject will remain in the study for safety follow up for 42 days after last dose of study drug or until AEs have resolved or become stable.

*Note that Subjects in Cohort 1 may not escalate above the initial 500 mg/m^2 starting dose and may have dose reductions based on safety only.

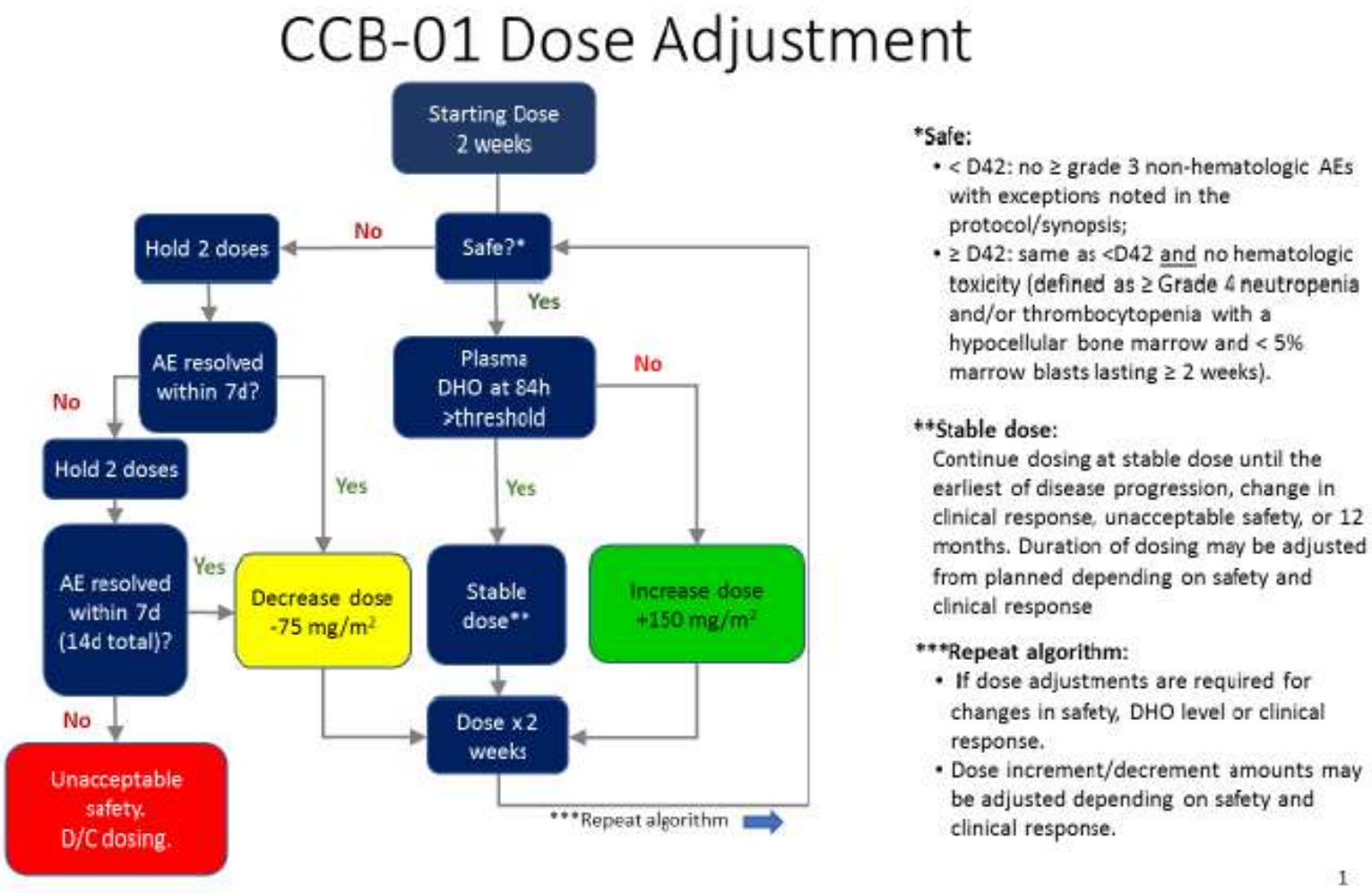

Figure 1. Dose Adjustment – Subject Level

7.6 Medication/AE Diary

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

7.7 Bone Marrow Biopsy

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the C2D8 visit ± 7 days, and one at Day 43 ± 7 days; thereafter, bone marrow sampling will be obtained every 12 weeks (or per institutional standard of care) and at the Final Visit. If a participant develops frank evidence of progression of AML during the course of treatment based on laboratory or clinical assessment, then he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at the Day 43 visit (defined as 43 days after initiating treatment or after 6 complete weeks after initiating study drug treatment regardless of number of doses), then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for the Day 43 visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

7.8 Flow Cytometry

Peripheral blood samples are to be obtained for flow cytometry in Cycle 1 at baseline (Day 1 pre-dose), Day 2 (24 hours after initiating treatment), and Day 3 (48 hours after initiating treatment).

7.9 Expansion Cohort

Once a dose has been reached that has an adequate DHO level (as mentioned above, “adequate” trough DHO may be adjusted after reviewing DHO level, safety and clinical response data) and acceptable safety/tolerability, approximately 15 subjects will be added starting at the highest safe/tolerated dose identified in the earlier cohorts. Decisions regarding adequacy of DHO threshold level will be made following review of these data from each cohort. These subjects are eligible for intra-subject dose adjustment (see Section 7.3.1 and Section 7.5).

The expansion cohort will follow the same visit procedures as the Maintenance Dose cohort (Section 8.5.4) and visit frequency may vary from 2 to 4 weeks per the investigator’s discretion.

7.10 Study Drug Discontinuation

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh), the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued if there is evidence of unacceptable safety/tolerability that does not resolve to ≤ Grade 2 within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 30 days after the last dose of brequinar or until they receive another treatment for their AML. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

7.11 Brequinar Pharmacokinetics (PK) / Dihydroorotate (DHO) Plasma Levels

Plasma samples for brequinar/DHO levels are to be obtained for each subject for the subject's first study dose (Cycle 1 Dose 1 for that subject). Sample scheduling is baseline at 0 hours (prior to dosing), and post dose at 1, 2, 4, 6, 24, 48, and 72 hours. Note that this schedule does not apply to Cycle 1 for subjects in the expansion cohort, see below.

A brequinar/DHO trough sample is to be obtained prior to dosing on Day 8 (C_{84h}, 84 hours after the Cycle 1 Day 4 dose) of Cycle 1, and prior to dosing on Days 1 and 8 of Cycles 2 and 3.

The 84-hour brequinar/DHO sample is to be repeated prior to dosing at the beginning of each 2-week cycle and at the Final Visit. This sampling schedule also applies for the expansion cohort subjects.

Directions regarding sample processing are presented in a separate laboratory manual.

7.12 Concomitant Medication/Treatment

The name, start date (if known), indication for use and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;
- Use of hydroxyurea for the purpose of leukemic cytoreduction may be allowed during the first 2 weeks of therapy if in the best interest of the participant and is approved by the medical monitor. Hydroxyurea can be used to treat leukocytosis if concurrent with and thought to be associated with presumed differentiation syndrome.

7.12.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

7.13 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

7.14 Storage, Stability, Labeling and Packaging

7.14.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

7.14.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-01

Contents: 100 or 250 mg Brequinar capsules

For oral use only. Take with approximately 8 ounces water every 3.5 days.

Subject Number: XX-XXXX

Treatment Duration: As directed

IND: 138355 Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

7.14.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution. No randomization codes are necessary for this open-label study.

7.14.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the Investigator's Brochure.

7.14.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the

next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

8 CONDUCT OF THE TRIAL

8.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

8.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

8.3 Institutional Review Board / Ethics Committees

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

8.4 Schedule of Events

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 14.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include: blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium).

Hematology tests include: hemoglobin, hematocrit, complete blood count with differential and platelet count.

In addition to the already scheduled weekly chemistry assessment during Cycles 1 and 2 for each subject, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.

8.5 Study Conduct

8.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study.
- Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

8.5.2 Cycle 1

Cycle 1 Day 1:

- Collect any adverse events or new concomitant medications since Screening.
- Draw samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP if >4 weeks since last test, and 12-lead ECG if >4 weeks since last test.
- Review results and confirm subject remains eligible for the study.
- Determine subject's starting dose based on the respective cohort mg/m^2 starting dose.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO sampling. Collect brequinar/DHO samples at 1, 2, 4, and 6 hours post dose.
- Process and store brequinar/DHO samples per the supplied laboratory manual.

- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- Enroll subject for text message reminders if the subject consents to that service.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual

Cycle 1 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Ship the flow cytometry sample per the supplied laboratory manual.

Cycle 1 Day 4:

- Collect 72h post dose brequinar/DHO samples. Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Process and store brequinar/DHO samples per the supplied laboratory manual.

Cycle 1 Day 8:

- Vital signs.
- Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Prior to the morning dose, collect brequinar/DHO samples (approximately 84h post the second dose of Cycle 1) and hematology/chemistry samples, then have subject take study medication.
- Process and store brequinar/DHO samples per the supplied laboratory manual.
- Notify DHO assay laboratory of incoming shipment and ship Cycle 1 brequinar/DHO samples (samples from Days 1, 2, 3, 4 and 8).

8.5.3 Cycle 2 (and any Dose Adjustment Cycle)

Repeat this visit as needed when dose adjustment is ongoing.

- Day 1:
  - Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Take vital signs and perform physical examination (including weight).
  - Collect pre-dose brequinar/DHO samples (approximately 84h post the fourth dose of the previous cycle) and hematology/chemistry samples.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.

- Review laboratory results/safety information and determine whether the subject should adjust the dose (based on acceptable safety and DHO level), continue with the current dose or hold study medication (unacceptable safety) per the guidelines below.
- If dosing will continue, dispense study medication.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)

- Day 8:
  - Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
  - Vital signs.
  - Collect pre-dose brequinar/DHO and hematology/chemistry samples.
  - Perform bone marrow sampling (window ±7 days).
  - If the subject is being dosed (i.e., has acceptable safety), have the subject take the morning dose.
  - If the subject's medication was held, review safety information and determine whether dosing can resume. If dosing can resume, determine dose, dispense adequate medication for 4 doses and have the subject take the morning dose.
  - Process and store brequinar/DHO samples per the supplied laboratory manual.
  - Continue to withhold study drug if safety remains unacceptable.
  - Dispense calendar/diary.
  - Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
  - Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples (samples from current cycle's Days 1 and 8).

Subjects may undergo dose adjustments at any time using the guidelines presented above except in Cohort 1. Subjects with acceptable safety can continue to escalate every 2 weeks by 150 mg/m^2 increments through 800 mg/m^2. Subjects with unacceptable safety can continue to undergo dose reductions of 75 mg/m^2 with no lower limit. Re-escalation to a dose previously shown as not tolerated for an individual subject is not permitted for these subjects.

Dose adjustments are permitted throughout the study for an individual subject based on safety, DHO level, and clinical response with an upper limit of 800 mg/m^2. This upper limit may be adjusted depending on safety/tolerability/DHO/brequinar PK or other factors during the study.

8.5.4 Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once a subject reaches a stable or maintenance dose (see Figure 1), the subject will be in the Maintenance Dose Cycle.

In the first 3 months from starting study drug, the Maintenance Dose Cycle procedures will occur every 2 weeks (with the exception of bone marrow sampling as discussed below). After completing 3 months from starting study drug, subjects may come to the clinic for a Maintenance Dose Cycle visit every 2 - 4 weeks per the investigator's discretion.

A subject may still move into a Dose Adjustment Cycle after a maintenance dose if required for a change in safety, DHO level or clinical response.

Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO and hematology/chemistry samples.
- Conduct physical examination and obtain vital signs; urine pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sampling (note that bone marrow is collected at the C2D8 visit (window ±7 days), at Day 43, then every 12 weeks or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity).
- Review the laboratory results/safety information and determine whether the subject should maintain current dose (acceptable safety) or hold study medication (unacceptable safety).
- Dispense study medication.
- Dispense calendar/diary.
- Manage text message reminders as needed (as a default do nothing, pause if study medication is put on hold, and restart if study medication is restarted)
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.

8.5.5 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination, vital signs, urine pregnancy test for WOCBP (if <4 weeks since previous), 12-lead ECG (if <4 weeks since previous), and bone marrow sampling (if > 4 weeks since previous bone marrow sample obtained).
- Review the safety information and determine whether the subject has acceptable safety or unacceptable safety.
- Notify DHO assay laboratory of incoming shipment and ship brequinar/DHO samples.
- Stop text message reminders.

8.5.6 Follow Up Visit (2 weeks after Final Visit)

- Contact subject two weeks after Final Visit to determine subject's survival status. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

8.5.7 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within four (4) weeks after the final dose.

8.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified window, it will not be necessary to file a protocol violation.

8.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

8.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

8.9 Short Messaging Service (SMS) Medication Reminders

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted in part to protect the security and privacy of protected health information (PHI). Covered entities (e.g.,

health care providers engaged in certain electronic transactions, health plans, and health care clearinghouses) that create, maintain, transmit, use, and disclose an individual's PHI are required to meet HIPAA requirements.

HIPAA's Privacy Rule restricts uses and disclosures of PHI, creates individual rights with respect to their PHI, and mandates administrative requirements. Among other requirements, the privacy rule requires a covered entity to reasonably safeguard PHI from any intentional or unintentional use or disclosure that is in violation of the requirements of HIPAA.

HIPAA's Security Rule requires covered entities to ensure confidentiality, integrity, and availability of its electronic PHI, to protect against reasonably anticipated threats or hazards to the security or integrity of its electronic PHI, to protect against reasonably anticipated impermissible uses and disclosure of its electronic PHI, and to ensure compliance by their workforce. Additionally, the Security Rule requires covered entities to put in place detailed administrative, physical, and technical safeguards to protect electronic PHI. To do this, covered entities are required to implement access controls and set up backup and audit controls for electronic PHI in a manner commensurate with the associated risk.

For protocol CCB-01, the Sponsor intends to utilize a third-party vendor with a HIPAA-compliant platform to send one-way text message reminders to study participants who have a mobile device. The SMS/text message will be sent on the days and times he or she is to take his or her study medication, e.g., Monday mornings and Thursday evenings. The exact timings of the reminders will be customized for each study participant. The PHI the third-party vendor receives will be restricted to the participant's mobile device number and study identification number. The study participant is not to reply to the text message except to "opt out" from the service by sending "STOP" in the message body. In any other case if he/she sends a text message, the texting service will reply with a message indicating that messages sent by participants are not being monitored. Study participants must agree to "opt in" for this service and can "opt out" at any time even if they initially agreed. Study participants will need to sign an addendum to the informed consent document documenting their decision prior to enrollment in the system (see Appendix 14.5).

The third-party vendor will sign an agreement with the Sponsor to use participant data only for the purposes of this study. Data will be purged from the vendor's servers at the conclusion of the trial upon written request by the Sponsor. Data will remain in the vendor's encrypted back-up files that will be maintained per HIPAA-compliant standards.

9 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs. Disease progression should not be reported as an AE unless worsening of signs and symptoms occur, or death from disease progression.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. If

the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.0* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

9.1 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

9.2 Classification of Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

9.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition ;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following a SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox@novellaclinical.com

MEDICAL MONITOR:	**Robert Sims, MD**
E-mail:	robert.sims@novellaclinical.com; YYA36071medmon@novellaclinical.com
Telephone:	614-721-2630
24-hour safety line:	1-866-758-2798 or 919-313-7111
Fax:	206-826-0483
Sponsor Representative:	**Barbara Powers, MSN, Ph.D.**
E-mail:	bpowers@clearcreekbio.com
Telephone:	484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

9.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

9.5 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring

of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

9.6 Hematologic Adverse Events

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's

life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

9.7 Management of Myelosuppression

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

9.8 Differentiation Syndrome

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
  - Control of leukocytosis with hydroxyurea;
  - Prompt administration of corticosteroids at a suggested dose of 10 mg of

dexamethasone IV every 12 hours until disappearance of symptoms and signs, continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated without dose reduction once the participant's clinical condition improves, upon discussion with the Sponsor.

9.9 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC < 25 x 10^9 /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100 x 10^9 /L or WBC < 25 x 10^9 /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100 x 10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).
- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 2 provides a flow chart for TLS monitoring.

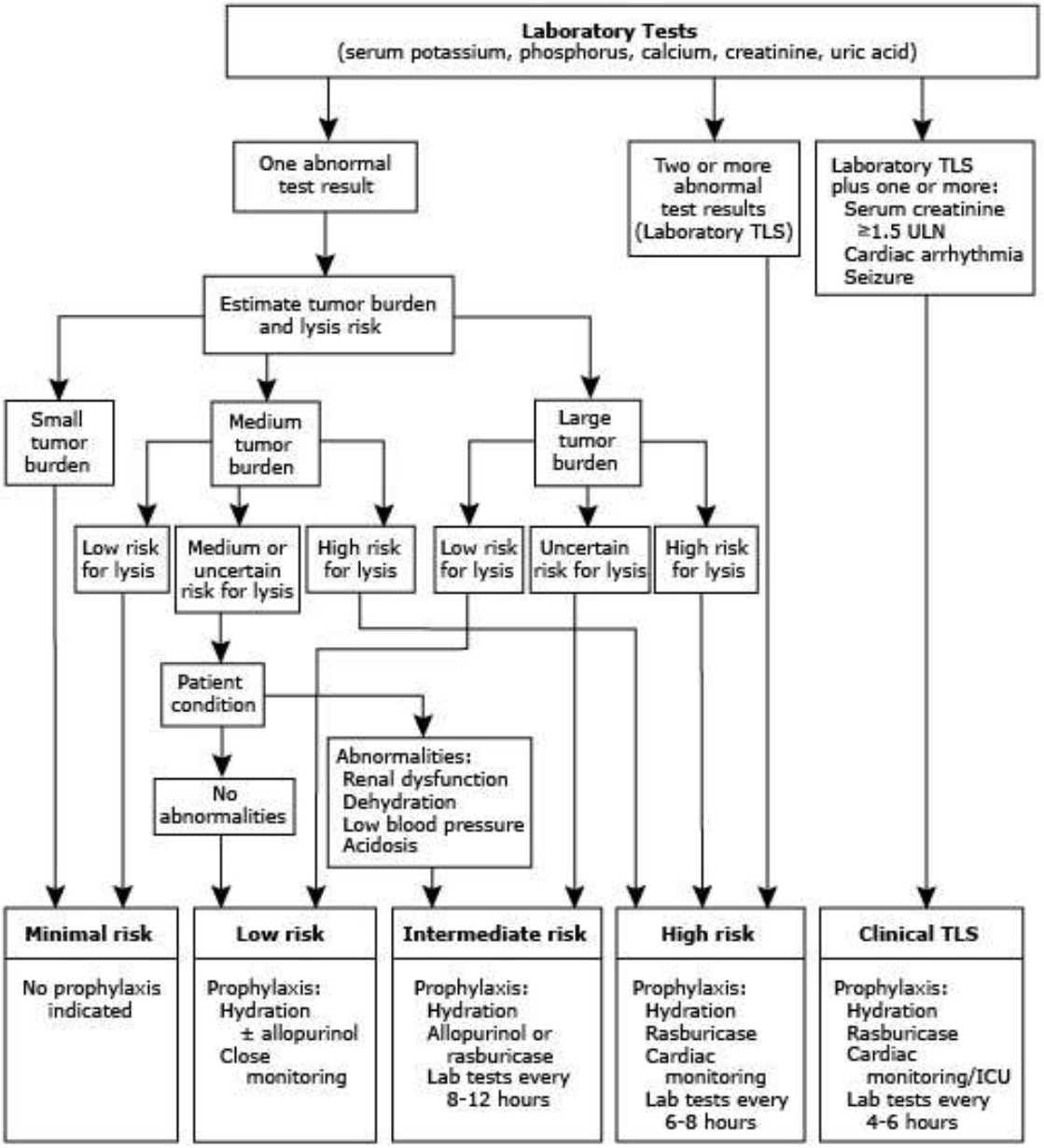

Figure 2. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

9.10 Infection Prophylaxis

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

9.11 Growth Factor Support

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

9.12 Management of Nausea, Vomiting, and Diarrhea

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

10 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

10.1 Study Populations for Analysis

The analysis sets are defined in Table 3.

Table 3. Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

10.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

10.3 Efficacy Analyses

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 4 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 4. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event

	endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

10.4 Other Endpoints

Brequinar Pharmacokinetics (PK)

Blood samples for PK analysis will be obtained at pre-specified times. Plasma PK parameters of brequinar including steady-state plasma concentration (Css); elimination half-life ($T_{1/2}$); Area under the concentration curve (AUC); systemic clearance (CL) and volume of distribution at steady state (Vss) will be estimated by compartmental and non-compartmental analysis (WinNonlin or similar).

Concentration data and PK parameters will be tabulated and summarized using descriptive

statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Blood samples for DHO analysis will be obtained at pre-specified times and will be summarized. Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

10.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will have 6 subjects; two additional cohorts of 3 subjects each will be added if adjustments are required to the cohort starting dose. The cohorts with 3 subjects may be expanded to 6 subjects depending on safety outcomes within the cohort. An expansion cohort of approximately 15 subjects will be enrolled with a starting dose of the highest tolerated starting dose from Cohorts 1 to 3.

10.6 Randomization

No randomization scheme is needed for this open label study.

10.7 Pooling of Study Centers

Not applicable to this small, early phase study.

10.8 Interim Analysis

No interim analysis is planned for this trial.

11 INVESTIGATOR RESPONSIBILITIES

11.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 14.6) to indicate commitment to comply with the contents.

11.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 11.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

11.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

11.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

11.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or

of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

11.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

11.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

12 SPONSOR RESPONSIBILITIES

12.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

12.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

12.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

12.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

12.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

12.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

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14 APPENDICES

14.1 APPENDIX A: CCB-01 Schedule of Events

CCB-01 Schedule of Events	**Screen[b]**	**Cycle 1 (Study Days 1 – 14)**					**Dose Adjustment Cycle (Cycle 2 and beyond as needed)**		**Maintenance Dose Cycle (no dose adjustment) Every 2 weeks**	**Final Visit**	**F/U Phone Call**	**Survival**
Procedures[a]		**D1**	**D2**	**D3**	**D4**	**D8**	**D1**	**D8**	**D1**		**Final Visit + 2 wks**	
Informed Consent[b]	X											
AE/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Medical history[c]	X											
Demographics[d]	X											
Physical Exam[d]	X	X					X		X	X		
Vital Signs[d]	X	X				X	X	X	X	X		
Pregnancy Test[e]	X								X	X		
ECOG Performance Status	X											
Hematology/Chemistry[f]	X	X				X	X	X	X	X		
Flow Cytometry[g]		X	X	X								
Chromosomal/mutational testing[h]	X											
12-lead ECG[b]	X								X	X		
MUGA/Echocardiogram	X											
Bone Marrow Sampling[i]	X							X		X		
Brequinar/DHO Plasma Sample[j]		X	X	X	X	X	X	X	X	X		
Biobanking samples[k]	X								X	X		
Ship DHO Plasma Samples						X		X	X			
Dispense/Collect Study Medication		X					X		X	X		
Dispense/Collect Subject Calendar/Diary		X					X		X	X		
Survival Assessment												X

a. Visit window of ± 1 day for dose escalation cycles; window of ± 3 days for non dose escalation cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <72h since Screening assessment. ECG and pregnancy test frequency are every 4 weeks or per institutional guidelines.
c. Medical history is to include AML diagnosis, previous AML treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Physical exam is to include weight.
e. For women of childbearing potential only, frequency is every 4 weeks or per institutional guidelines.
f. In addition to the already scheduled weekly chemistry assessment during Cycles 1 and 2 for each subject, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.
g. Flow cytometry testing of peripheral blood is to be obtained at 0 (pre-dose C1D1), and post dose at 24 and 48 hours.
h. Testing panel is per institutional standard of care; obtain sample at Screening.
i. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking for possible further analysis from Screening, Day 43, and Final Visit (or bone marrow sample closest to Final Visit). Perform bone marrow sampling at screening, at study Day 22 (C2D8), at Day 43, and once every 12 weeks after a stable dose has been reached. Timing of this procedure may be adjusted to ensure results are available for the next clinic visit. Procedure window is ±7 days.
j. Brequinar/DHO plasma sampling schedule: Cycle 1: 0 (pre-dose), post dose 1, 2, 4, 6, 24, 48, 72 hours and C1D8 pre-dose (+84h after C1D4 dose); Cycle 2 and adjustment cycles: pre-dose Days 1 and 8; every 2-week Maintenance Cycle until 3-months on drug: pre-dose Day 1 and every 2 to 4 week Maintenance Dose Cycle beyond 3-months on drug. Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Cycle 2 and beyond plasma brequinar/DHO draws ±4h. Ensure trough samples (e.g., C1D1, C2D1, C3D1) are obtained prior to dosing. Plasma samples for brequinar/DHO for expansion cohort are to be obtained prior to dosing on Day 1 of each 2-week cycle for the first 3 cycles, then every 12 weeks.
k. Biobanking samples (bone marrow) are to be collected whenever bone marrow sampling is performed.

14.2 APPENDIX B: ECOG Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14.3 APPENDIX C: Brequinar/DHO Plasma Sampling

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Brequinar and DHO plasma samples are to be obtained at the following time points (±30 minutes through 6h, then ±2h for the 24h, 48h, 72h and 84h samples:

	Cycle 1									Cycle 2*		Maintenance Dose Cycle	Final Visit
	D1					D2	D 3	D 4	D8	D1	D8	D1	
Time Point	Pre-dose	1h	2h	4h	6h	24h	48h	72h	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose	84h after prev. dose

*Or any cycle where the brequinar dose has been adjusted from the previous 2-week dose.

14.4 APPENDIX D: Common Terminology Criteria for Adverse Events (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

14.5 APPENDIX E: Sample Subject Consent Form

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 2.0 04June2018>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will take the study medication about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

Cycle 1 Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children, and 12-lead ECG.

- If you qualify for the study and still choose to participate, you will be given adequate study medication for 2 weeks (4 doses).
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Cycle 1 Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- **Cycle 1 Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit. You will take your second dose of study medication this evening.
- **Cycle 1 Day 8**:

At this visit, you will:

- Have your vital signs checked.
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Take your next dose of study medication in the clinic.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.

Cycle 2

You will return to the clinic 2 weeks after starting the study medication. The study team may adjust your dose of study medication (you may be given more or less of the drug) depending on your safety results, laboratory, and DHO levels. This visit may be repeated as needed if your dose adjustment continues.

- **Day 1**:
  - Your unused study medication will be collected (if you have any), and your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
  - Your vital signs will be checked and a physical examination performed.
  - Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.

- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given adequate medication for another 2 weeks (4 doses). Take your next dose of study medication in the clinic.

- **Day 8:**

At this visit, you will:

- Have your vital signs checked.
- Have a bone marrow sample (window ±7 days).
- Before you take your morning dose, you will have blood samples taken for brequinar/DHO and hematology/chemistry.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will continue to take the medication dispensed to you.

Maintenance Dose Cycle (visit every 2 - 4 weeks)

Once you have reached a "stable dose" where no more dose adjustments seem to be needed, you will return to the clinic every 2 weeks and have the procedures below. After you've been taking the study medication for 3 months, your study doctor may space your visits out to every 4 weeks.

Day 1:

At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for pre-dose brequinar/DHO and hematology/chemistry.
- Have a physical examination, vital signs, urine pregnancy test for women able to bear children, 12-lead ECG.
- Have a bone marrow sampling (the bone marrow aspiration sampling is performed at study Day 22 ±7 days, at study Day 43 and repeated every 12 weeks or more often if there is a safety concern).
- Your study team will review the laboratory results/safety information and determine whether you should stay at the same dose or whether you should temporarily stop taking the study medication or whether the dose should be changed.
- If you are not having any side effects that may indicate it is not safe for you to continue taking the study medication, you will be given additional medication and continue to take the medication dispensed to you as directed by the study team.
- Your diary/calendar will be collected and a new one provided to you.

Final Visit

This visit is to take place if you or your study team decide you should stop participation in the study or you have reached 12 months of study participation. At this visit, you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for brequinar/DHO, and hematology/chemistry.

- Have a physical examination (including weight), vital signs, urine pregnancy test for women able to bear children, 12-lead ECG and bone marrow sampling (unless it has been less than 4 weeks since the previous bone marrow sampling).
- Turn in any unused study medication.
- Turn in your calendar/diary.

Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by phone to be asked about any new medical events or new or changed medications since your last clinic visit.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea
- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.
- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.
- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.
- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.
- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to

the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

Addendum to Informed Consent for Short Messaging Service (SMS/text)

Reminders for Protocol CCB-01

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Addendum ICF Version 1.0 31May2018>

WHY AM I BEING ASKED TO SIGN THIS ADDENDUM TO THE CONSENT?

You are being asked to sign this addendum to the consent because you have agreed to participant in study CCB-01 and because it is very important for you to take your study medication at the correct times (e.g., Monday mornings and Thursdays evenings). One effective way to help you remember to take your medication on time is for you to receive a text reminder on your phone. The sponsor of the study (Clear Creek Bio, Inc.) is using an external vendor to generate a text message reminder that will be sent to your mobile device when it is time for you to take your study medication.

VOLUNTARY NATURE OF THIS SERVICE

It is entirely optional for you to receive this service. Your decision to receive text message reminders for your medications will not in any way affect your ability to enroll in the study. You may also "opt out" at any time by responding "STOP" to the messages, or by contacting your study team.

DESCRIPTION OF THE NATURE OF THE DATA YOU WILL PROVIDE
You will provide your mobile device number to the study team who will then enter the number into the third-party vendor's system for sending out the text reminders.

DESCRIPTION OF HOW THE DATA WILL BE USED
The only information that will be shared with the third-party vendor is your mobile device number and your study participant identification number. The system is set up so that one-way messages are sent from the service to you. You should not reply to the messages you receive except to "opt out". If you do send a message, the texting service will reply with a message indicating that the messages you may send are not being monitored.

WHAT WILL THE MESSAGE SAY?
On the twice-weekly schedule (i.e., Monday mornings and Thursday evenings), you will receive a text with the following information: “It is time for you to take your CCB-01 study medication. Thank you for participating in this study.” You may delete this message after reading.

DESCRIPTION OF HOW THIS DATA WILL BE SECURELY MANAGED
The mobile device number you provide to be used for these reminders will be managed in a manner that ensures the best possible security. The mobile device number will not be shared with any other third-party vendor or the sponsor of this study (Clear Creek Bio, Inc.).

WHAT IF I DON’T HAVE A PHONE THAT CAN RECEIVE TEXT MESSAGES?
If you do not have a mobile phone or cannot receive text messages, you cannot participate in receiving these text message reminders.

DISCLOSURES OF RISKS AND VULNERABILITIES
Although unlikely, it is possible that the unencrypted text messages you receive could inadvertently be seen by someone else. Because the messages are de-identified (your name will not appear), the most information that could be seen would be that you are participating in a study. You are not sending any information back to the third-party vendor, so nothing you send could be seen by mistake.

The study team members are not responsible for any loss or breach of data that results from something beyond their control, e.g., you lose your mobile device containing text messages reminders, or a third-party vendor or host experiences a server/data breach.

Standard text/data messaging rates apply to these messages, and because some mobile phone providers charge an additional fee for the sending and receiving of text messages, you might be charged additionally by your mobile phone provider if you choose to receive the text message reminders.

PROCESS FOR NOTIFYING PARTICIPANT IN CASE OF AN ACTUAL OR POTENTIAL SECURITY BREACH

If the third-party vendor that has your mobile device number experiences a breach or a potential breach, the third-party vendor will notify the sponsor of this study, Clear Creek Bio, Inc. The sponsor will notify the study team at each participating institution, and the study team will contact you regarding the possible risks associated with the breach/potential breach regarding your mobile device number.

Consent Form SMS/Text Addendum Signature

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for receiving text message medication reminders for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary in this text messaging service and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the study team and third-party vendor to have access to my mobile device number.	
4. I agree to take part in the mobile device text message reminder for the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

APPENDIX F: WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health

care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat

to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

14.6 Appendix G: Investigator's Statement and Agreement

STUDY NUMBER: CCB-01

STUDY TITLE: 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)

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

Site Address: _____

_____

_____

_____

CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development Barbara L. Powers Digitally signed by Barbara L. Powers, MSN, PhD DN: cn=Barbara L. Powers, MSN, PhD, o=Clear Creek Bio, Inc., ou=Clinical Operations, email=bpowers@clearcreekbio.com, c=US Date: 2019.05.06 15:09:40 -04'00' PRINT NAME: Barbara Powers, MSN, Ph.D.	Date: 06 May 2019
Research & Development David P Hesson, PhD Digitally signed by David P Hesson, PhD Date: 2019.05.06 16:29:11 -04'00' PRINT NAME: David P. Hesson, Ph.D.	Date: 06 May 2019
Chemistry and Manufacturing/Quality David P. Hesson, PhD Digitally signed by David P. Hesson, PhD Date: 2019.05.06 16:29:44 -04'00' PRINT NAME: David P. Hesson, Ph.D.	Date: 06 May 2019
Sponsor Representative Vikram Sheel Kumar PRINT NAME: Vikram Sheel Kumar, MD	Date: 06 May 2019

Revision History/Amendments:

Version Number	Date
1.0	31 May 2018
2.0	04 June 2018
3.0	04 October 2018
4.0	11 October 2018
5.0	16 October 2018
6.0	30 April 2019

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)

Study No: CCB-01

Version Date: 30 April 2019

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal Dose$_{(10\%, 50\%, 90\%)}$
LPS	Lipopolysaccharide
M	Molar
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar

Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

2 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	● To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. ● To characterize the pharmacokinetic (PK) profile of brequinar. ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. ● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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. Subject dosing will be adjusted based on safety/tolerability, brequinar pharmacokinetics, and DHO levels. Up to 27 subjects are planned to be entered in this trial. Although Cohort 1 was planned to have 6 subjects, enrollment in this cohort was stopped after 5 subjects when brequinar PK and DHO results became available; these results led to changes in study design as described in this section. 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. Subjects in Cohort 2 will be dosed starting with 500 mg/m^2 once-weekly. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 once-weekly dose. Brequinar PK and DHO samples will also be obtained during Week 2, and the Week 2 results will be used to make decisions about the Week 3 dose frequency (once- or twice-weekly) and dose. The dose is to be adjusted for each subject to meet the twice-weekly brequinar PK and 72h 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 72h DHO level meet criteria described in the Individual Dose Adjustment Guidelines (below), the subject may move to twice-weekly dosing on a continuing basis as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria also described in the Guidelines for Individual Dose Adjustment. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	● Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	● Rates of treatment-emergent adverse events. ● Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. ● Event free survival (EFS). ● Duration of response. ● PK profile of brequinar. ● DHO plasma profile.

Exploratory endpoints:	● 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
Sample Size:	Up to 27 subjects
Number of Sites:	3 – 6
Study Period:	An enrollment period of 18 - 24 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial. 2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification who have exhausted available therapy. 3. ECOG Performance Status 0 to 2. 4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2. 5. Adequate hepatic function (unless deemed to be related to underlying leukemia). 1. Direct bilirubin ≤ 2 x ULN 2. ALT ≤ 3 x ULN 3. AST ≤ 3 x ULN 6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation. 7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time. 8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating

	physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration. 9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.
Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 4. Pre-existing liver disease. 5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 7. Active cerebrospinal involvement of AML. 8. Diagnosis of acute promyelocytic leukemia (APL) 9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 12. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

Treatment	This is an open-label study of dose-adjusted brequinar for the treatment of AML. Brequinar is supplied as 100 mg or 250 mg oral capsules which will be used to dose subjects on a mg/m^2 basis as described in the Guidelines for Individual Dose Adjustment section below.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: • Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study. • Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications. • Physical examination (including weight). • Vital signs (heart rate, respiratory rate, blood pressure, body temperature). • Pregnancy test for women of childbearing potential (WOCBP). • ECOG performance assessment. • Hematology/chemistry. • 12-lead ECG with QTcF. • Standard chromosomal and mutational testing per institutional guidelines. • Bone marrow sampling • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available. **Dose Adjustment: Cycle 1 Week 1** **Week 1 Day 1**: • Collect any adverse events or new concomitant medications since Screening. • Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. • Conduct physical examination (including weight) if >4 weeks since last performed, vital signs, urine pregnancy test for WOCBP if >4 weeks since last test, and 12-lead ECG if >4 weeks since last test. • Review results and confirm subject remains eligible for the study.

	• Dispense study medication. • Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose. • Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. • Enroll subject for text message reminders if the subject consents to that service; initiate when subject reaches twice-weekly dosing. **Week 1 Day 2**: Collect 24h post dose brequinar/DHO and flow cytometry samples. **Week 1 Day 3**: Collect 48h post dose brequinar/DHO and flow cytometry samples. **Week 1 Day 4**: Collect 72h post dose brequinar/DHO and flow cytometry samples. **Week 1 Day 5**: Collect 96h post dose brequinar/DHO/flow cytometry samples. **Week 1 Day 6**: Collect 120h post dose brequinar/DHO and flow cytometry samples. **Dose Adjustment: Cycle 1 Week 2** The Cycle 1 Week 2 procedures are to be followed to move to twice-weekly dosing using brequinar exposure and 72h DHO. This week's procedures may be repeated weekly as necessary until the twice-weekly dose is determined. **Week 2 Day 1:** • Vital signs. • Check the diary/elicit information about AEs/new concomitant medications since the last visit. • Check results of previous week's brequinar PK and DHO levels to determine if dose adjustment is needed to move to twice-weekly dosing. • Prior to the morning dose, collect brequinar/DHO/flow cytometry samples and hematology/chemistry samples, then have subject take study medication. **Week 2 Day 2**: Collect 24h post dose brequinar/DHO and flow cytometry samples. **Week 2 Day 3**: Collect 48h post dose brequinar/DHO and flow cytometry samples.

	Week 2 Day 4: Collect 72h post dose brequinar/DHO and flow cytometry samples. **Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)** Once a subject reaches a twice-weekly dose, the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria. Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only). **Maintenance Dose Cycle Day 1:** • Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. • Collect pre-dose brequinar/DHO, hematology/chemistry, and flow cytometry sample. • Obtain vital signs; urine pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ± 7 days), at the Week 7 visit (Day 43 ± 7 days), then every 12 weeks ± 7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity. • If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL). • Dispense study medication. • Dispense calendar/diary. • Begin twice-weekly text message reminders. **Maintenance Dose Cycle Day 8 (up to Week 12):** • Collect pre-dose brequinar/DHO/flow cytometry sample. • Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).

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Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO/flow cytometry and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct urine pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed.
- Ensure all adverse events have been recorded.
- Stop text message reminders.

Telephone Follow Up Visit (2 weeks after Final Visit)

Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.

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<tr><td>Safety/
Tolerability</td><td>

Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting toxicity (DLT) during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.

If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Exceptions to Grade 3 Nonhematologic AEs

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.

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	<table><tr><td>Diarrhea</td><td>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.</td></tr><tr><td>Laboratory abnormalities</td><td>Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.</td></tr><tr><td>Mucositis</td><td>Grade 3 with duration < 1 week</td></tr><tr><td>Fatigue</td><td>Grade 3 with duration < 2 weeks</td></tr></table> For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject. **Hematologic Toxicity** After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.
Cohort Starting Doses	Cohort 1 enrollment was stopped after treating 5 subjects at 500 mg/m^2 twice weekly to allow data review and analysis. No dose escalation was permitted for Cohort 1 subjects. Due to extensive study design changes a sixth subject will not be enrolled into Cohort 1. All subjects will have a starting dose of 500 mg/m^2 once-weekly. Cohort 2 will treat approximately 6 subjects with this starting dose once-weekly, which may be adjusted to twice-weekly with an adjusted dose (if needed) based on brequinar PK and DHO levels. Each subject's dosing frequency and dose may be adjusted as shown below.
Expansion Cohort	An expansion cohort of up to 15 subjects will be added to obtain further information on safety, brequinar exposure, and DHO levels.
Guidelines for Individual Dose Adjustment	Cohort 1 is now complete; all subjects were dosed with 500 mg/m^2 twice-weekly. Starting with Cohort 2, subjects will have a starting dose of 500 mg/m^2 and initially take oral brequinar once-weekly for at least two weeks (two total doses). Brequinar pharmacokinetics (BRQ PK) and dihydroorotate (DHO) levels from each week will be used to determine the next week's dose using the algorithm shown in the table

below. Additional weeks of once-weekly dosing are permitted as needed to adjust the dose until the criteria have been met or the dosing limits have been reached (minimum 200 mg/m^2, maximum 800 mg/m^2). If BRQ PK adjustments lead to a previously tested dose, accept the highest previously tested dose with 24h BRQ PK < 5 mcg/mL and move to the 72h DHO assessment. Do not reassess BRQ PK criteria after moving to the 72h DHO assessment. After the dose has been adjusted (if necessary) to meet BRQ PK and 72h DHO criteria, subjects may move to twice-weekly dosing (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis.

Algorithm to Set Twice-Weekly Dose

Brequinar PK*	72h DHO**	Action
24h BRQ PK < 5 mcg/mL	NA	Increase dose 150 mg/m^2 and continue weekly dosing, reassess BRQ PK
48h BRQ PK > 5 mcg/mL	NA	Decrease dose 150 mg/m^2 and continue weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose 75 mg/m^2 and continue weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 3 or after

* Brequinar PK (BRQ PK) Criteria: 24h BRQ PK ≥ 5 mcg/mL AND 48h BRQ ≤ 5 mcg/mL; if BRQ PK adjustments lead to a previously tested dose, accept the highest previously tested dose with 24h BRQ PK < 5 mcg/mL and move to the 72h DHO assessment.

**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL

After the twice-weekly dose has been determined using the above criteria, the twice-weekly dose may be further adjusted using the 84h DHO (trough) algorithm shown below. The 84h DHO level obtained at the beginning of each week will be used to adjust the next week's dose as needed. This dose adjustment may be made each week through Week 12 and every two weeks after Week 12, if necessary.

Algorithm to Adjust Twice-Weekly Dose using 84h DHO

84h DHO (Trough)	Action
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly through Week 12 then every 2 weeks. Adjust dose prn per 84h DHO criteria.
84h DHO ≥ 5000 ng/mL	HOLD. Notify subject not to take next dose. Hold dosing for one week. Decrease next week's dose by 75 mg/m^2. Resume twice-weekly dosing.

	Each subject will continue twice-weekly dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels. Subjects who discontinue due to unacceptable safety/tolerability or die due to disease progression prior to the Day 43 visit may be replaced. The dose adjustment procedures may be revised after safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed.
Brequinar/DHO	Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule: • Cycle 1 Week 1: Day 1 (prior to dosing, and 1, 2, 4, and 6 hours), Days 2, 3, 4, 5, and 6 (24h, 48h, 72h, 96h, and 120h after dosing) • Cycle 1 Week 2: Day 1 prior to dosing, Days 2, 3, and 4 (24h, 48h, and 72h after dosing); this week's schedule is to be repeated as necessary to meet BRQ PK and 72h DHO criteria. • After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12, then every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle). • Final Visit: obtain brequinar, DHO, and flow cytometry samples.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP. Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last

	dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

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3 INTRODUCTION

3.1 BACKGROUND: ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10% (SEER, 2015 [1]). It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

3.2 DIHYDROOROTATE DEHYDROGENASE (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous, essential enzyme. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

3.3 BREQUINAR

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was

selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was

reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

3.4 RATIONALE FOR THE PLANNED TRIAL

This study is designed to obtain safety and efficacy data for brequinar in patients with AML.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in detail in Section 8.5.

3.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-weekly administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a twice-weekly schedule of brequinar dosed approximately every 84 hours, while measuring brequinar PK and plasma DHO to fine-tune the dose that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see Brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggest that a starting dose for Cohort 1 of 500 mg/m^2 p.o. will be safe and well-tolerated in subjects with AML. Each subject's subsequent dosing may be adjusted depending on the safety, tolerability, brequinar PK, and DHO level obtained during the period following dose adjustment. See Section 8.4.

3.5 RISK/BENEFIT OF BREQUINAR

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of AML is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment in patients with AML is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with AML typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

3.6 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

In studies utilizing the weekly schedule of administration in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the

guidelines presented in Section 10.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and treatment are described in Sections 10.10 and 10.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 10.7.

3.7 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal drug-drug interaction studies have been performed with medications commonly used in treating AML, however nonclinical *in vitro* studies have confirmed there is no CYP interaction or CYP induction associated with brequinar use. The nonclinical studies have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies performed to date.

3.8 STEPS TO BE TAKEN TO CONTROL OR MITIGATE RISKS

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 10.

4 TRIAL OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML.

4.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

4.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

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

5 TRIAL DESIGN

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 may be adjusted based on safety/tolerability, brequinar pharmacokinetics (PK), and DHO levels.

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

All subjects will now start with 500 mg/m^2 once weekly. Cohort 2 will enroll approximately 6 subjects followed by an expansion cohort of approximately 15 subjects. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 once-weekly dose. Brequinar PK and DHO samples will also be obtained during Week 2, and the Week 2 results will be used to make decisions about the Week 3 dose frequency (once- or twice-weekly) and dose. The dose is to be adjusted for each subject to meet the twice-weekly brequinar PK and 72h 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 72h DHO level meet criteria described in Section 8.5.1, the subject may move to twice-weekly dosing as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria described in Section 8.5.2.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in detail in Section 8.

6 TRIAL ENDPOINTS

6.1 PRIMARY ENDPOINT

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

6.2 SECONDARY ENDPOINTS

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

6.3 EXPLORATORY ENDPOINTS

- 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

7 TRIAL POPULATION

7.1 NUMBER OF SUBJECTS

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

7.2 INCLUSION CRITERIA

1. Willing and able to provide written informed consent for the trial.
2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification who have exhausted available therapy.
3. ECOG Performance Status 0 to 2.
4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2.
5. Adequate hepatic function (unless deemed to be related to underlying leukemia).
    a. Direct bilirubin ≤ 2 x ULN
    b. ALT ≤ 3 x ULN
    c. AST ≤ 3 x ULN
6. Adequate renal function as documented by creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time.
8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.
9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

7.3 EXCLUSION CRITERIA

1. Patients in need of immediate leukapheresis.
2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.

3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.
4. Pre-existing liver disease.
5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:
    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.
6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).
7. Active cerebrospinal involvement of AML.
8. Diagnosis of acute promyelocytic leukemia (APL).
9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.
10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.
11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
12. Nursing women or women of childbearing potential (WOCBP) with a positive urine pregnancy test.

7.4 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

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

All subjects will start with 500 mg/m^2 once weekly. Cohort 2 will enroll approximately 6 subjects followed by an expansion cohort of approximately 15 subjects. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 once-weekly dose. Brequinar PK and DHO samples will also be obtained during Week 2, and the Week 2 results will be used to make decisions about the Week 3 dose frequency (once- or twice-weekly) and dose. The dose is to be adjusted for each subject to meet the twice-weekly brequinar PK and 72h 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 72h DHO level meet criteria described in Section 8.5.1, the subject may move to twice-weekly dosing as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria described in Section 8.5.2.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters.

Dosing will continue for 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.

8.1 DESCRIPTION OF BREQUINAR

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis and will be adjusted based on tolerability, safety, brequinar PK, and DHO levels. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 24 hours. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

8.2 TREATMENT ADMINISTRATION

Five subjects were enrolled in the now-completed Cohort 1. All subjects were dosed with twice weekly brequinar 500 mg/m^2 for a range of 2 to 16 doses (one to 8 weeks). No additional subjects will be enrolled into Cohort 1.

Starting with Cohort 2, subjects will initially take oral brequinar once weekly for at least two weeks (two total doses). Brequinar exposure and DHO levels will be used to adjust the brequinar dose (if necessary) to meet brequinar PK and 72h DHO criteria described in Section 8.5.1. Subjects may

then move to twice-weekly dosing (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis. The brequinar dose may be further adjusted if needed using the 84h DHO (trough) Criteria shown in Section 8.5.2. Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. Each dose will generally consist of multiple capsules; the capsules do not need to be swallowed all at once but can be spread over up to 15 minutes as needed. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar/DHO samples and results needed for dosing adjustments. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

8.3 SAFETY/TOLERABILITY

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Cohort 1 had a fixed starting dose of 500 mg/m^2 with no dose escalation permitted. Cohort 2 and the expansion cohort will start with 500 mg/m^2 once-weekly and have adjustments made to dose and dose frequency using safety/tolerability, brequinar exposure (PK), and DHO levels. Safety at the subject level is defined in Section 8.3.1; hematologic toxicity is defined in Section 8.3.2.

The following adverse events are commonly observed in patients with AML and should be differentiated from possible adverse effects of brequinar: fatigue, fever, thrombocytopenia and other cytopenias, infection, pallor, shortness of breath, weight loss, night sweats, and anorexia. Any of these events can be serious in nature and may result in death. Disease progression of AML is considered a lack of efficacy rather than an adverse event. Death from disease progression is to be reported as presented in Section 10.

Adverse events commonly observed in patients treated with brequinar are provided in the Investigator's Brochure and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 subjects treated once-weekly (DuP 785-012), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In most instances, drug related toxicities were clinically manageable and reversible upon discontinuation of brequinar treatment. In a study where brequinar was dosed twice-weekly to solid tumor subjects, no drug-related deaths occurred. Stomatitis/mucositis was observed in 13 of the 19 (68%) patients across all doses. Mild to moderate (Grades 1 and 2) stomatitis was observed in 10 patients with a more severe (Grade 3) stomatitis seen in 3 patients at doses over 600 mg/m^2. One patient at 600 mg/m^2 had drug discontinuation due to drug-related stomatitis. Myelosuppression was the main dose-limiting toxicity (DLT) with thrombocytopenia (Grades 1-4), observed after 2 to 9 doses above 600 mg/m^2. Any of these events reported with brequinar use can be serious in nature and may result in death.

Prescriptions can be provided in advance for supportive care for common brequinar-related AEs such as mucositis.

8.3.1 Safety/Tolerability – Subject Level

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered a DLT during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in Table 8-1.

If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled visits and assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Table 8-1. Exceptions to Grade 3 Nonhematologic AEs

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 completion of the first 42 days of treatment, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for at least one week (i.e., two doses if twice-weekly) for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

8.3.2 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

8.4 COHORT STARTING DOSES

Cohort 1 enrollment was stopped after treating 5 subjects at 500 mg/m^2 twice weekly to allow data review and analysis. No dose escalation was permitted for Cohort 1 subjects. Due to extensive study design changes a sixth subject will not be enrolled into Cohort 1.

All subjects will have a starting dose of 500 mg/m^2 once-weekly. Cohort 2 will treat approximately 6 subjects with this starting dose once-weekly, which may be adjusted to twice-weekly with an adjusted dose (if needed) based on brequinar PK and DHO levels. Each subject's dosing frequency and dose may be adjusted as shown in the following sections.

8.5 INDIVIDUAL DOSE ADJUSTMENT GUIDELINES

Cohort 1 is now complete; all subjects were dosed with 500 mg/m^2 twice weekly.

Starting with Cohort 2, subjects will have a starting dose of 500 mg/m^2 and initially take oral brequinar once weekly for at least two weeks (two total doses). Brequinar pharmacokinetics (BRQ PK) and dihydroorotate (DHO) levels from each week will be used to determine the next week's dose using the algorithm shown in the tables below. Additional weeks of once-weekly dosing are permitted as needed to adjust the dose until the criteria have been met or the dosing limits have been reached (minimum 200 mg/m^2, maximum 800 mg/m^2). If BRQ PK adjustments lead to a previously tested dose, accept the highest previously tested dose with 24h BRQ PK < 5 mcg/mL and move to the 72h DHO assessment. Do not reassess BRQ PK criteria after moving to the 72h DHO assessment. After the dose has been adjusted (if necessary) to meet BRQ PK and 72h DHO criteria, subjects may move to twice-weekly dosing (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis.

The dose adjustment procedures may be revised after each preceding cohort's safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed.

8.5.1 Brequinar Exposure (BRQ PK) and 72h DHO Criteria to Set Twice-Weekly Dosing

All subjects in Cohort 2 will begin with 500 mg/m^2 dosed once weekly. A second weekly dose is administered at either 500 mg/m^2 or an adjusted dose. Additional weekly doses may be administered if dose adjustment is needed to meet the twice-weekly criteria. Pre-clinical evidence (Sykes et al., 2016 [4]) suggests that a twice-weekly dose is most likely to lead to efficacy, therefore the goal is to adjust the dose to allow all subjects to dose on a twice-weekly basis. In order to move to twice-weekly dosing both the brequinar exposure (BRQ PK) and 72h DHO criteria as described below must be met. The maximum allowable dose is 800 mg/m^2; the minimum allowable dose is 200 mg/m^2. If BRQ PK adjustments shown in Table 8-2 and Figure 8-1 below lead to a dose previously tested in this subject, accept the highest previously tested dose for this subject that resulted in 24h BRQ PK < 5 mcg/mL and move to the 72h DHO assessment.

Dose increases must first meet acceptable safety requirements as described in Section 8.3.1. If unacceptable safety occurs, hold dosing until AE resolves to ≤ grade 2, reduce dose by 150 mg/m^2 and resume dosing. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available.

Table 8-2. Algorithm to Set Twice-Weekly Dose

Brequinar PK*	72h DHO**	Action
24h BRQ PK < 5 mcg/mL	NA	Increase dose 150 mg/m^2 and continue weekly dosing, reassess BRQ PK
48h BRQ PK > 5 mcg/mL	NA	Decrease dose 150 mg/m^2 and continue weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose 75 mg/m^2 and continue weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 3 or after

* Brequinar PK (BRQ PK) Criteria: 24h BRQ PK ≥ 5 mcg/mL AND 48h BRQ ≤ 5 mcg/mL; if BRQ PK adjustments lead to a previously tested dose, accept the highest previously tested dose with 24h BRQ PK < 5 mcg/mL and move to the 72h DHO assessment.

**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL

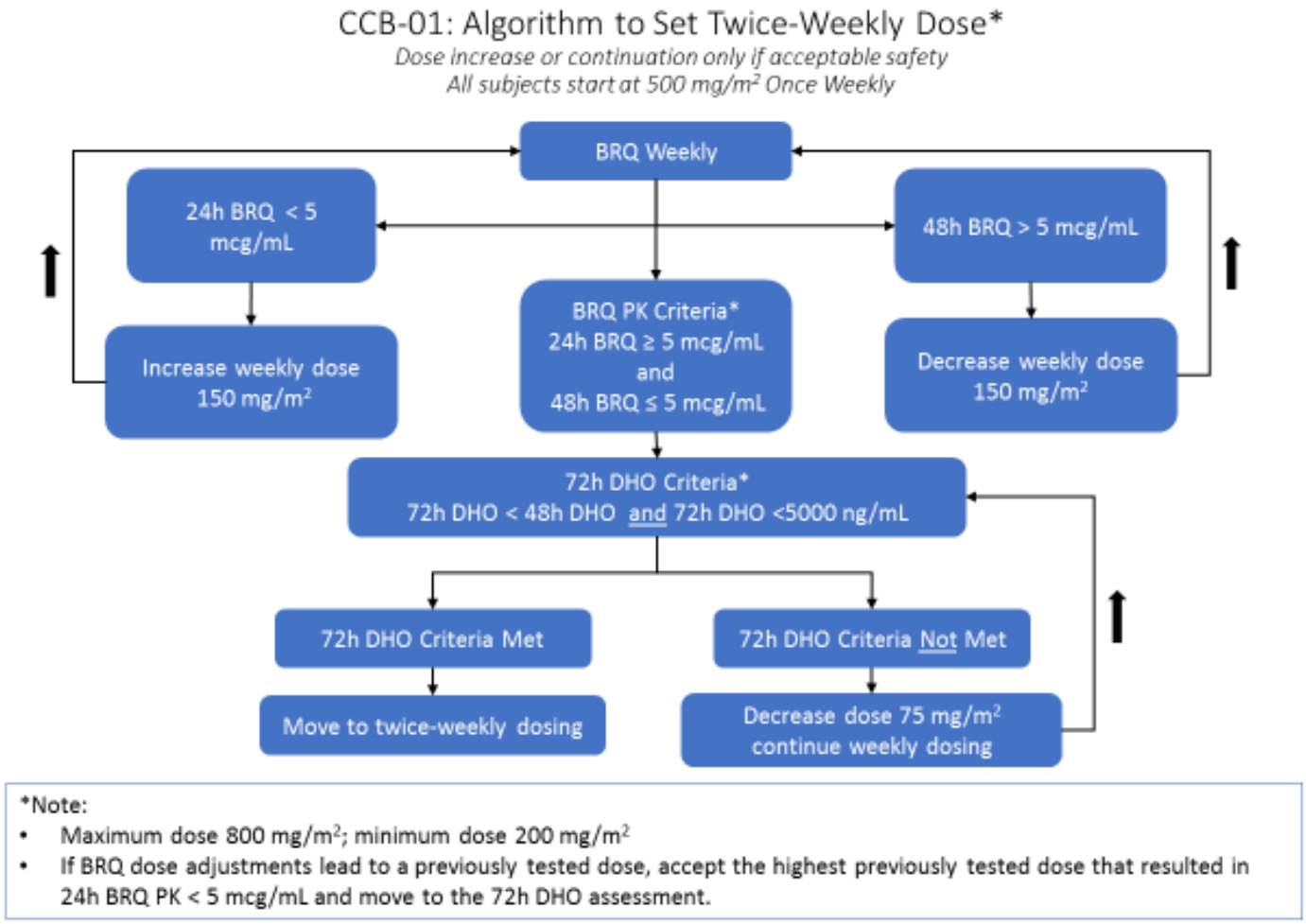

Figure 8-1. Algorithm to Set Twice-Weekly Dose

8.5.2 Dose Adjustment Using 84h DHO

After the twice-weekly dose has been determined using the above criteria, the twice-weekly dose may be further adjusted using the 84h DHO (trough) algorithm shown below. The 84h DHO level obtained prior to the first dose of each week will be used to adjust the next week's dose as needed. This dose adjustment may be made each week through Week 12 and every two weeks after Week 12, if necessary. If DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available.

Table 8-3. Algorithm to Adjust Twice-Weekly Dose using 84h DHO (Trough)

84h DHO Criteria	Action
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly x 12 weeks then every 2 weeks. Adjust dose PRN per 84h DHO criteria.
84h DHO ≥ 5000 ng/mL	HOLD. Notify subject not to take next dose. Hold dosing for one week. Decrease next week's dose by 75 mg/m^2. Resume twice-weekly dosing.

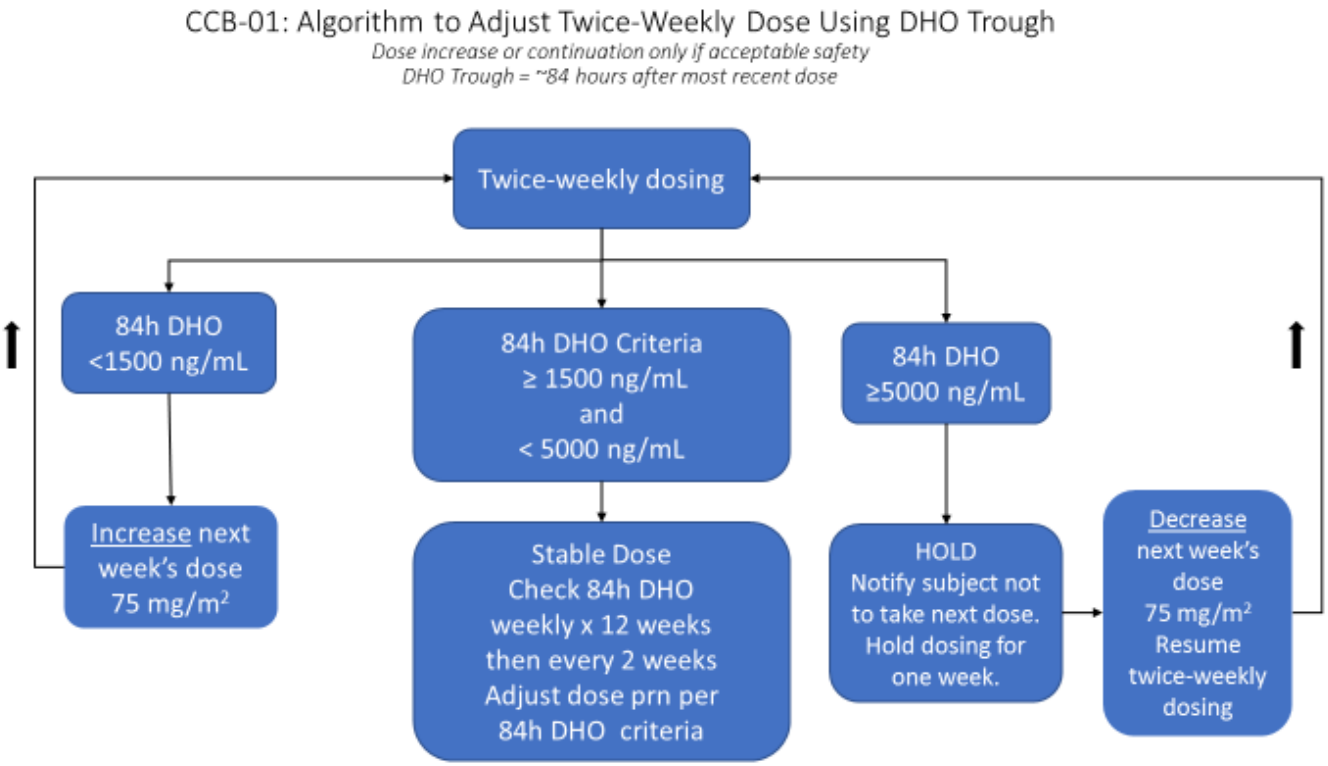

Figure 8-2. Algorithm to Adjust Dose Using 84h DHO

Each subject will continue twice-weekly dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels. Subjects who discontinue due to unacceptable safety/tolerability or die due to disease progression prior to the Week 7 (Day 43) visit may be replaced.

8.6 MEDICATION/AE DIARY

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

8.7 BONE MARROW BIOPSY

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the Week 4 visit (Day 22 ± 7 days), and one at the Week 7 visit (Day 43 ± 7 days); thereafter, bone marrow sampling will be obtained every 12 weeks ± 7 days (or per institutional standard of care) and at the Final Visit. If a participant develops frank evidence of progression of AML during the course of treatment based on laboratory or clinical assessment, he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at Visit 7 (Day 43) (defined as 43 days after initiating treatment or after 6 complete weeks after initiating study drug treatment regardless of number of doses), then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for any visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

8.8 EXPANSION COHORT

Following completion of Cohort 2, an expansion cohort of up to 15 subjects will be added to further define the dosing, BRQ PK and DHO criteria and assess the safety, tolerability, and biological activity of the dosing scheme.

The expansion cohort will follow the same visit procedures as Cohort 2.

8.9 STUDY DRUG DISCONTINUATION

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh) at or prior to Visit 7 (43 days), the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued for an individual subject if there is evidence of unacceptable safety/tolerability that does not resolve to ≤ Grade 2 within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 14 days after the last dose of brequinar or until they receive another treatment for their AML. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

8.10 BREQUINAR PHARMACOKINETICS (PK)/DIHYDROOROTATE (DHO) PLASMA LEVELS/FLOW CYTOMETRY

Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule and as shown in Section 15.3:

- Cycle 1 Week 1: Day 1 (prior to dosing, and 1, 2, 4, and 6 hours), Days 2, 3, 4, 5, and 6 (24h, 48h, 72h, 96h, and 120h after dosing)
- Cycle 1 Week 2: Day 1 prior to dosing, Days 2, 3, and 4 (24h, 48h, and 72h after dosing); this week's schedule is to be repeated as necessary until BRQ PK and 72h DHO criteria have been met.
- After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12, then once every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle).
- Final Visit: obtain brequinar, DHO, and flow cytometry samples.

The samples will be processed and shipped per the instructions in the laboratory manual. If the samples are drawn on a weekend, holiday, or after hours, obtain the samples on the specified study day and ship the samples as soon as possible. Directions regarding sample processing and shipping are presented in a separate laboratory manual.

8.11 CONCOMITANT MEDICATION/TREATMENT

Record the name, start date, indication for use, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;
- Use of supportive care measures per institution's standard of care are permitted at any time including hydroxyurea for the purpose of leukemic cytoreduction.

Transfusions are to be recorded beginning from up to 2 weeks prior to first dose of study drug and ongoing throughout the individual's participation.

8.11.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

8.12 TREATMENT COMPLIANCE

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

8.13 STORAGE, STABILITY, LABELING AND PACKAGING

8.13.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.13.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-01

Contents: 100 or 250 mg Brequinar capsules

For oral use only. Take with approximately 8 ounces water every 3.5 days.

Subject Number: XX-XXXX

Treatment Duration: As directed

IND: 138355 Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.13.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist per the designated mg/m^2 dose for each subject. No randomization codes are necessary for this open-label study.

8.13.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the protocol and the Investigator's Brochure or are commonly associated with AML. The event will be considered expected if commonly associated with AML in the opinion of the investigator or Medical Monitor even if not specifically listed in these documents.

8.13.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

9 CONDUCT OF THE TRIAL

9.1 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

9.2 INFORMED CONSENT

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

9.3 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEES

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's Brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 SCHEDULE OF EVENTS

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), and lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential and platelet count, and peripheral blast count.

In addition to the already scheduled chemistry assessments, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.

9.5 STUDY CONDUCT

9.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study.
- Pertinent medical/surgical history (including AML diagnosis and laboratory and clinical evidence of progression, previous AML treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF.
- Standard chromosomal and mutational testing per institutional guidelines.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

9.5.2 Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available.

9.5.3 Dose Adjustment: Cycle 1 Week 1

Week 1 Day 1

- Collect any adverse events or new concomitant medications since Screening.
- Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, urine pregnancy test for WOCBP if >4 weeks since last test and 12-lead ECG if >4 weeks since last test.
- Review results and confirm subject remains eligible for the study.

- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- Enroll subject for text message reminders if the subject consents to that service; initiate when subject reaches twice-weekly dosing.

Week 1 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples.

Week 1 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples.

Week 1 Day 4:

- Collect 72h post dose brequinar/DHO samples and flow cytometry samples.

Week 1 Day 5:

- Collect 96h post dose brequinar/DHO/flow cytometry samples.

Week 1 Day 6:

- Collect 120h post dose brequinar/DHO samples and flow cytometry samples.

9.5.4 Dose Adjustment: Cycle 1 Week 2

The Cycle 1 Week 2 procedures are to be followed to move to twice-weekly dosing using brequinar exposure and 72h DHO. This week's procedures may be repeated weekly as necessary until the twice-weekly dose is determined.

Week 2 Day 1:

- Vital signs.
- Check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Check results of previous week's brequinar PK and DHO levels to determine if dose adjustment is needed to move to twice-weekly dosing.
- Prior to the morning dose, collect brequinar/DHO/flow cytometry samples and hematology/chemistry samples, then have subject take study medication.

Week 2 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples.

Week 2 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples.

Week 2 Day 4:

- Collect 72h post dose brequinar/DHO samples and flow cytometry samples.

9.5.5 Maintenance Dose Cycle

Once a subject reaches a twice-weekly dose (see Table 8-2 and Figure 8-2), the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria.

Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only).

Maintenance Dose Cycle Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO, hematology/chemistry samples, and flow cytometry sample.
- Obtain vital signs; urine pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ±7 days), at the Week 7 visit (Day 43 ±7 days), then every 12 weeks ±7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity).
- If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).
- Dispense study medication.
- Dispense calendar/diary.
- Begin text message reminders.

Maintenance Dose Cycle Day 8 (up to Week 12)

- Collect pre-dose brequinar/DHO, and flow cytometry sample.
- Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO <1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).

9.5.6 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO/flow cytometry and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct urine pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed.
- Ensure all adverse events have been recorded.
- Stop text reminders.

9.5.7 Telephone Follow Up Visit (2 weeks after Final Visit)

- Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

9.5.8 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.

9.6 COMPLIANCE WITH STUDY PROCEDURES

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified windows, it will not be necessary to file a protocol deviation.

9.7 EARLY WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;

- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

9.8 EARLY TERMINATION OF THE STUDY

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 SHORT MESSAGING SERVICE (SMS) MEDICATION REMINDERS

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted in part to protect the security and privacy of protected health information (PHI). Covered entities (e.g., health care providers engaged in certain electronic transactions, health plans, and health care clearinghouses) that create, maintain, transmit, use, and disclose an individual's PHI are required to meet HIPAA requirements.

HIPAA's Privacy Rule restricts uses and disclosures of PHI, creates individual rights with respect to their PHI, and mandates administrative requirements. Among other requirements, the privacy rule requires a covered entity to reasonably safeguard PHI from any intentional or unintentional use or disclosure that is in violation of the requirements of HIPAA.

HIPAA's Security Rule requires covered entities to ensure confidentiality, integrity, and availability of its electronic PHI, to protect against reasonably anticipated threats or hazards to the security or integrity of its electronic PHI, to protect against reasonably anticipated impermissible uses and disclosure of its electronic PHI, and to ensure compliance by their workforce. Additionally, the Security Rule requires covered entities to put in place detailed administrative, physical, and technical safeguards to protect electronic PHI. To do this, covered entities are required to implement access controls and set up backup and audit controls for electronic PHI in a manner commensurate with the associated risk.

For protocol CCB-01, the Sponsor intends to utilize a third-party vendor with a HIPAA-compliant platform to send one-way text message reminders to study participants who have a mobile device. The SMS/text message will be sent on the days and times he or she is to take his or her twice-weekly study medication, e.g., Monday mornings and Thursday evenings. The exact timings of the reminders will be customized for each study participant. The PHI the third-party vendor receives will be restricted to the participant's mobile device number and study identification number. The study participant is not to reply to the text message except to "opt out" from the service by sending "STOP" in the message body. In any other case if he/she sends a text message,

the texting service will reply with a message indicating that messages sent by participants are not being monitored. Study participants must agree to “opt in” for this service and can "opt out" at any time even if they initially agreed. Study participants will need to sign an addendum to the informed consent document documenting their decision prior to enrollment in the system (see Appendix 15.5).

The third-party vendor will sign an agreement with the Sponsor to use participant data only for the purposes of this study. Data will be purged from the vendor's servers at the conclusion of the trial upon written request by the Sponsor. Data will remain in the vendor's encrypted back-up files that will be maintained per HIPAA-compliant standards.

If requested by the subject and permitted by the institution’s IRB, a designated caregiver may be texted instead of the subject.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the End of Study and Death forms.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

10.1 CLASSIFICATION OF CAUSALITY

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

10.2 CLASSIFICATION OF SEVERITY

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.3 SERIOUS ADVERSE EVENT (SAE) REPORTING

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

Death due to disease progression is considered to be an Expected event in these patients with relapsed/refractory AML and does not require reporting on an expedited basis.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox.biotech@iqvia.com

MEDICAL MONITOR: **Robert Sims, MD**
E-mail: robert.sims@iqvia.com

YYA36071medmon@iqvia.com
Telephone: 614-721-2630
24-hour safety line: 1-866-758-2798 or 919-313-7111
Fax: 206-826-0483

Sponsor Representative: **Barbara Powers, MSN, Ph.D.**
E-mail: bpowers@clearcreekbio.com
Telephone: 484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

10.5 PREGNANCIES

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or

subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.6 HEMATOLOGIC ADVERSE EVENTS

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

10.7 MANAGEMENT OF MYELOSUPPRESSION

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

10.8 DIFFERENTIATION SYNDROME

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
  - Control of leukocytosis with hydroxyurea;
  - Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs, continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated once the participant's clinical condition improves, upon discussion with the Sponsor and Medical Monitor.

10.9 TUMOR LYSIS SYNDROME (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC $< 25 \times 10^9$ /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100 x 10^9 /L or WBC $< 25 \times 10^9$ /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100 x 10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).
- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 10-1 provides a flow chart for TLS monitoring.

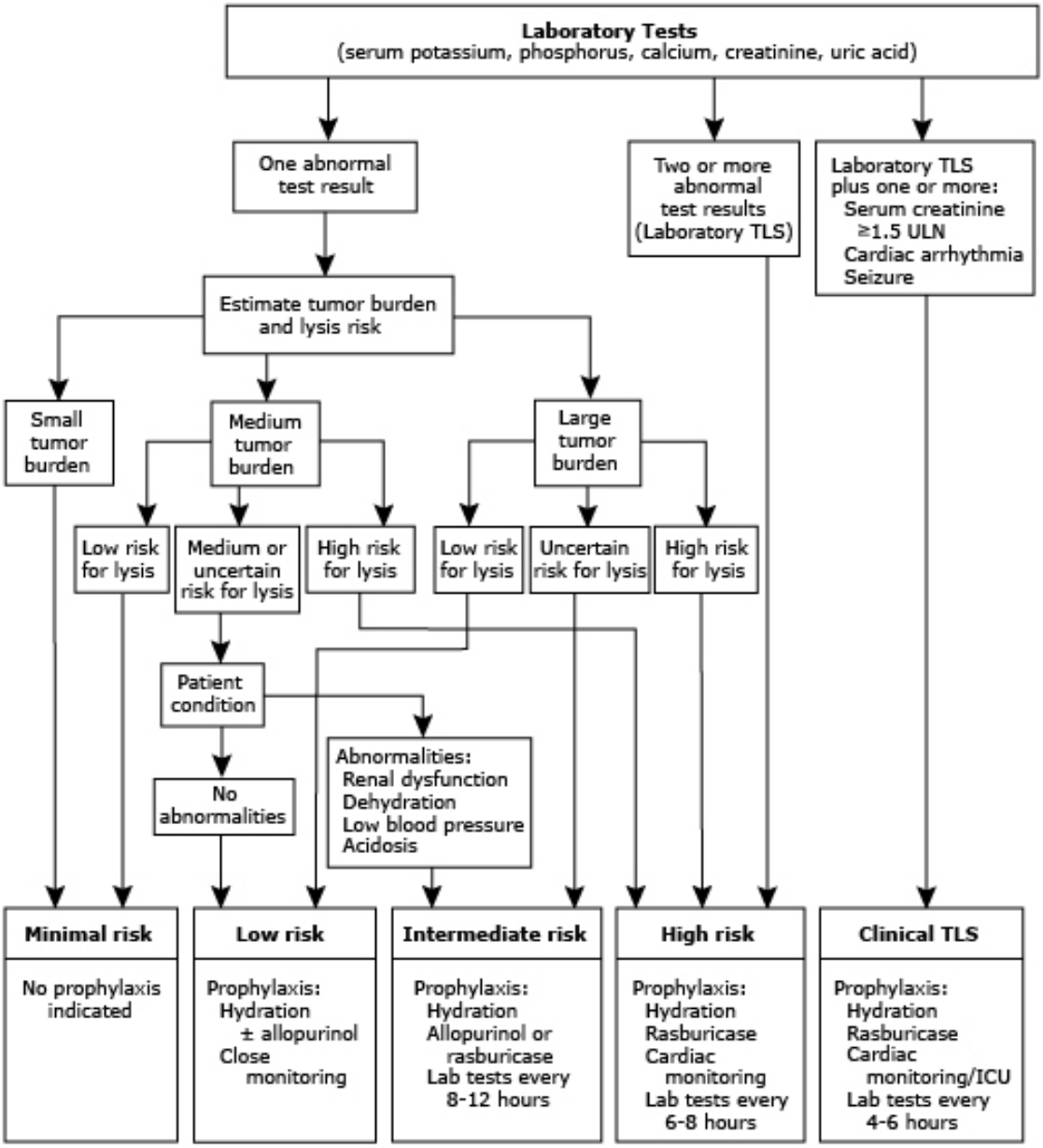

Figure 10-1. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

10.10 INFECTION PROPHYLAXIS

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

10.11 GROWTH FACTOR SUPPORT

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

10.12 MANAGEMENT OF NAUSEA, VOMITING, AND DIARRHEA

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 STUDY POPULATIONS FOR ANALYSIS

The analysis sets are defined in Table 11-1.

Table 11-1. Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

11.2 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

11.3 EFFICACY ANALYSES

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 11-2 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 11-2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses may be performed for the above secondary endpoints from first dose of brequinar. Censoring rules for time-to-event endpoints will be

	described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response
    - Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.
- Platelet response
    - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

11.4 OTHER ENDPOINTS

Brequinar Pharmacokinetics (PK) and DHO Levels

Blood samples for brequinar PK and DHO analyses will be obtained at pre-specified times. The following plasma parameters may be analyzed (including but not limited to): concentration maximum (C_{max}), time of peak concentration (T_{max}) elimination half-life ($T_{1/2}$), and area under the concentration curve (AUC) estimated by compartmental and non-compartmental analysis (WinNonlin or similar). Additional parameters may be added as necessary.

Concentration data, PK and DHO parameters will be tabulated and summarized using descriptive

statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

11.5 SAMPLE SIZE CONSIDERATIONS

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will had up to 6 subjects; Cohort 2 will have approximately 6 subjects. An expansion cohort of approximately 15 subjects will be enrolled to further refine brequinar PK and DHO criteria and to further assess the safety, tolerability, and biological activity of this dosing scheme.

11.6 RANDOMIZATION

No randomization scheme is needed for this open label study.

11.7 POOLING OF STUDY CENTERS

Not applicable to this small, early phase study.

11.8 INTERIM ANALYSIS

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 INVESTIGATOR'S PERFORMANCE

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 15.6) to indicate commitment to comply with the contents.

12.2 CONFIDENTIALITY

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 SOURCE DOCUMENTATION

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 DATA COLLECTION

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

12.5 CASE REPORT FORMS, INVESTIGATOR'S SITE FILE AND RECORD RETENTION

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or

of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 NON-PROTOCOL RESEARCH

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 PUBLICATION

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 GENERAL

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

13.2 INDEMNITY

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 DATA MONITORING

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 AUDIT

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 CONFIDENTIALITY

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 FINANCE

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

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15 APPENDICES

15.1 APPENDIX A: CCB-01 SCHEDULE OF EVENTS

CCB-01 Schedule of Events **Procedures[a]**	**Screen[b]**	**Cycle 1 Week 1**		**Cycle 1 Week 2[j]**		**Maintenance Dose Cycle**	**Final Visit**	**F/U Phone Call**	**Survival**
		D1	**D2 -D 6**	**D1**	**D2 – D4**	**D1 & D8**		**Final Visit + 2 wks**	
Informed Consent[b]	X								
AE/Concomitant Medications	X	X	X	X	X	X	X	X	
Medical history[c]	X								
Demographics[d]	X								
Physical Exam[d]	X	X		X			X		
Vital Signs[d]	X	X		X		X	X		
Pregnancy Test	X					X q 4 weeks	X		
ECOG Performance Status	X								
Hematology/Chemistry[e]	X	X		X		X (D1 only)	X		
Chromosomal/mutational testing[f]	X								
12-lead ECG	X					X q 4 weeks	X		
Bone Marrow Sampling[g, h]	X					X q 12 weeks	X		
Biobanking samples[g]	X					X	X		
Brequinar/DHO/Flow Cytometry Sample[h]		X	X	X	X	X	X		
Ship DHO Plasma Samples[i]			X (D4)	X	X (D4)	X	X		
Dispense/Collect Study Medication		X		X		X	X		
Dispense/Collect Subject Calendar/Diary		X		X		X	X		
Survival Assessment									X

a. Visit window of ± 1 day for Cycle 1 visits; window of ± 3 days for Maintenance Dose cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <72h since Screening assessment. ECG and pregnancy test frequency are every 4 weeks or per institutional guidelines.
c. Medical history is to include AML diagnosis, previous AML treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Complete physical examination and vital signs once every 4 weeks or more often if needed to assess an AE.
e. If additional complete blood count (CBC) with differential results are available (for example, daily reports when a subject is hospitalized), these results may be captured in the eCRF using an Unscheduled visit.
f. Testing panel is per institutional standard of care; obtain sample at Screening.
g. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking for possible further analysis from Screening, Week 7 (Day 43), and Final Visit. Perform bone marrow sampling at screening, at Visit 4 (Day 22), Visit 7 (Day 43), then once every 12 weeks. Timing of this procedure may be adjusted to ensure results are available for the next clinic visit. Procedure window is ±7 days.
h. Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.
i. Process, store and ship these samples per the Laboratory Manual.
j. Cycle 1 Week 2 procedures are to be repeated weekly until a twice-weekly dose has been determined.

15.2 APPENDIX B: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15.3 APPENDIX C: BREQUINAR/DHO/FLOW CYTOMETRY SAMPLING

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.

Brequinar and DHO plasma samples and peripheral blood for flow cytometry are to be obtained at the following time points:

	Cycle 1 Week 1									
	D1					D2	D 3	D 4	D 5	D 6
Time Point	Pre-dose	1h	2h	4h	6h	24h	48h	72h	96h	120h

	Cycle 1 Week 2 (or week adjusting dose using Brequinar Exposure & 72h DHO Criteria)			
	D1	D2	D 3	D 4
Time Point	Pre-dose	24h	48h	72h

	Maintenance Cycle (Day 8 through Week 12 only)	
	D1	D8
Time Point	Pre-dose ~84h after previous dose	Pre-dose ~84h after previous dose

15.4 APPENDIX D: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

15.5 APPENDIX E: SAMPLE SUBJECT CONSENT FORM

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 3.0 30 April 2019>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will begin the study by taking the study medication once a week for at least 2 weeks. After the results of certain blood tests are known (level of study drug and the enzyme being tracked in this study), the dose may be adjusted and your schedule may be changed to twice-weekly or about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings for the remainder of the time you are participating in the study. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle.

Cycle 1 Week 1

- **Week 1 Day 1:**

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.

- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and choose to participate, you will be given study medication to take while at this clinic visit.
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Week 1 Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 Day 5**: You will come back to the clinic approximately 96 hours (4 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 Day 6**: You will come back to the clinic approximately 120 hours (5 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.

Cycle 1 Week 2 (or any week when dose is adjusted for brequinar PK criteria)

You will come to the clinic weekly during the dose adjustment period that uses brequinar PK and DHO blood levels. This week's procedures will be repeated weekly as necessary until the twice-weekly dose is determined. You may need only one week of these procedures.

Week 2 Day 1: At this visit you will come to the clinic to have blood samples taken for brequinar/DHO and flow cytometry. Your diary will be checked for any new medical events, new medications or a change in dose of any medications since the last visit. You will take your second dose of study medication.
Week 2 Day 2: At this visit you will come to the clinic to have blood samples taken for brequinar/DHO and flow cytometry.
Week 2 Day 3: At this visit you will come to the clinic to have blood samples taken for brequinar/DHO and flow cytometry.
Week 2 Day 4: At this visit you will come to the clinic to have blood samples taken for brequinar/DHO and flow cytometry.

Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)

Once you reach a twice-weekly dose, you will be in the Maintenance Dose Cycle.

In the first 12 weeks from starting study drug (after finding twice-weekly dosing), the Maintenance Dose Cycle procedures will occur every week on Day 1 and Day 8. After completing 12 weeks from starting study drug, you may come to the clinic for a Maintenance Dose Cycle visit once every 2 weeks (Day 1 only).

Maintenance Dose Cycle Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination every 4 weeks (including weight) (unless within one week of Screening), vital signs, urine pregnancy test for women able to bear children once every 4 weeks, a 12-lead ECG once every 4 weeks, and a bone marrow sample every 12 weeks.
- Take the first dose of the week at the clinic; if you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week; if beyond Week 12, adequate medication will be provided for the entire two-week cycle.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

Maintenance Dose Cycle Day 8:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, and flow cytometry.
- Take the first dose of the week at the clinic.
- If you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.
- You will not need to have this visit after Week 12.

Final Visit

This visit is to take place when you are leaving the study. You will:

- Be asked about any new medical events or new or changed medications since your last visit.

- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination (including weight), vital signs, urine pregnancy test for women able to bear children if more than 4 weeks since the last test, 12-lead ECG if more than 4 weeks since the last test, and bone marrow sample if more than 4 weeks since the last test.
- Any leftover study medication will be collected.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications.
- If you signed up for text message reminders these will be stopped.

Telephone Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by telephone approximately two weeks after Final Visit to inquire if any new adverse events have occurred. Survival information will be collected while you are participating in the study (i.e., up to 2 weeks after last dose of study medication).

Unscheduled Visits

You may ask to come to the clinic when needed to be seen for unscheduled visits and tests to assess any new medical events providing the onset occurs within two (2) weeks after you have taken the final dose of study medication.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia/hemorrhage (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea

- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Infections
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

Some of these side effects were severe enough in patients treated with brequinar to require hospitalization or caused death. In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause a condition called differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.
- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.
- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.
- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.
- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to

the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

Addendum to Informed Consent for Short Messaging Service (SMS/text)

Reminders for Protocol CCB-01

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Addendum ICF Version 3.0 30 April 2019>

WHY AM I BEING ASKED TO SIGN THIS ADDENDUM TO THE CONSENT?

You are being asked to sign this addendum to the consent because you have agreed to participant in study CCB-01 and because it is very important for you to take your study medication at the correct times (e.g., Monday mornings and Thursdays evenings). One effective way to help you remember to take your medication on time is for you to receive a text reminder on your phone. The sponsor of the study (Clear Creek Bio, Inc.) is using an external vendor to generate a text message reminder that will be sent to your mobile device when it is time for you to take your study medication.

VOLUNTARY NATURE OF THIS SERVICE

It is entirely optional for you to receive this service. Your decision to receive text message reminders for your medications will not in any way affect your ability to enroll in the study. You may also "opt out" at any time by responding "STOP" to the messages, or by contacting your study team.

DESCRIPTION OF THE NATURE OF THE DATA YOU WILL PROVIDE
You will provide your mobile device number to the study team who will then enter the number into the third-party vendor's system for sending out the text reminders.

DESCRIPTION OF HOW THE DATA WILL BE USED
The only information that will be shared with the third-party vendor is your mobile device number and your study participant identification number. The system is set up so that one-way messages are sent from the service to you. You should not reply to the messages you receive except to "opt out". If you do send a message, the texting service will reply with a message indicating that the messages you may send are not being monitored.

WHAT WILL THE MESSAGE SAY?
On the twice-weekly schedule (i.e., Monday mornings and Thursday evenings), you will receive a text with the following information: “It is time for you to take your CCB-01 study medication. Thank you for participating in this study.” You may delete this message after reading.

DESCRIPTION OF HOW THIS DATA WILL BE SECURELY MANAGED
The mobile device number you provide to be used for these reminders will be managed in a manner that ensures the best possible security. The mobile device number will not be shared with any other third-party vendor or the sponsor of this study (Clear Creek Bio, Inc.).

WHAT IF I DON’T HAVE A PHONE THAT CAN RECEIVE TEXT MESSAGES?
If you do not have a mobile phone or cannot receive text messages, you cannot participate in receiving these text message reminders.

MAY I DESIGNATE A CAREGIVER TO RECEIVE THESE MESSAGES?
If you do not have a mobile phone, you may designate a caregiver to receive these messages on your behalf and pass them on to you.

DISCLOSURES OF RISKS AND VULNERABILITIES
Although unlikely, it is possible that the unencrypted text messages you receive could inadvertently be seen by someone else. Because the messages are de-identified (your name will not appear), the most information that could be seen would be that you are participating in a study. You are not sending any information back to the third-party vendor, so nothing you send could be seen by mistake.

The study team members are not responsible for any loss or breach of data that results from something beyond their control, e.g., you lose your mobile device containing text messages reminders, or a third-party vendor or host experiences a server/data breach.

Standard text/data messaging rates apply to these messages, and because some mobile phone providers charge an additional fee for the sending and receiving of text messages, you might be charged additionally by your mobile phone provider if you choose to receive the text message reminders.

PROCESS FOR NOTIFYING PARTICIPANT IN CASE OF AN ACTUAL OR POTENTIAL SECURITY BREACH

If the third-party vendor that has your mobile device number experiences a breach or a potential breach, the third-party vendor will notify the sponsor of this study, Clear Creek Bio, Inc. The sponsor will notify the study team at each participating institution, and the study team will contact you regarding the possible risks associated with the breach/potential breach regarding your mobile device number.

Consent Form SMS/Text Addendum Signature

SUBJECT'S DATE OF BIRTH: _____/_____/_____
mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for receiving text message medication reminders for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary in this text messaging service and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the study team and third-party vendor to have access to my mobile device number.	
4. I agree to take part in the mobile device text message reminder for the above study.	

By signing this consent form, I have not given up any of my legal rights.

Printed Name of Subject	Signature of Subject	Date	**Time**
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

15.6 APPENDIX F: WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health

care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat

to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

15.7 APPENDIX G: INVESTIGATOR'S STATEMENT AND AGREEMENT

STUDY NUMBER: CCB-01

STUDY TITLE: 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)

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

Site Address: _____

_____

_____

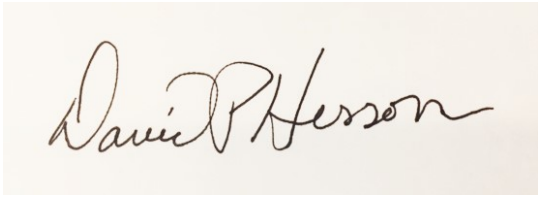
_____

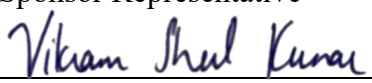
CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development 	Date: 27FEB2020
PRINT NAME: BARBARA L. POWERS, MSN, PH.D.	

Research & Development 	Date: 27FEB2020
PRINT NAME: DAVID P. HESSON, PH.D.	

Chemistry and Manufacturing/Quality 	Date: 27FEB2020
PRINT NAME: DAVID P. HESSON, PH.D.	

Sponsor Representative 	Date: 27FEB2020
PRINT NAME: VIKRAM SHEEL KUMAR, MD	

Revision History/Amendments:

Version Number	Date
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6.0	30 April 2019
7.0	21 February 2020

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)

Study No: CCB-01

Version Date: 21 February 2020

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
BLL	Bi-lineal leukemia
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal $Dose_{(10\%, 50\%, 90\%)}$
LPS	Lipopolysaccharide
M	Molar
MPAL	Mixed phenotypic acute leukemia

Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar
Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
t½	Half-Life
T-ALL	T-cell lymphoblastic leukemia
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

2 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses.
Primary Objective	● To determine the safety and tolerability of brequinar and the DHODH inhibitory level of brequinar in adult patients with AML and other hematological malignancies.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner 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. ● To characterize the pharmacokinetic (PK) profile of brequinar ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
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 predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment. ● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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 and other hematological malignancies. The study will also assess the inhibition of DHODH and the PK profile of brequinar in plasma. Subject dosing will be adjusted based on safety/tolerability, brequinar pharmacokinetics, and DHO levels.

	Up to 27 subjects are planned to be entered in this trial. Although Cohort 1 was planned to have 6 subjects, enrollment in this cohort was stopped after 5 subjects when brequinar PK and DHO results became available; these results led to changes in study design as described in this section. The sixth subject will not be enrolled in Cohort 1. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly. Although the 500 mg/m^2 starting dose of brequinar was well tolerated by some subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses lower than 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, newly enrolled Cohort 2 subjects will now start with 350 mg/m^2 once weekly. Approximately 3 additional subjects will be enrolled into Cohort 2 and may be followed by an expansion cohort of approximately 6-12 subjects. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 dose and schedule. Subjects who meet the twice weekly brequinar PK and 72h DHO criteria in Week 1 may proceed to twice weekly dosing with 350 mg/m^2 in Week 2. Subjects whose brequinar PK and DHO levels do not meet the twice weekly criteria will decrease the dose to 200 mg/m^2 once weekly. For subjects requiring the dose decrease, brequinar PK and DHO samples will also be obtained daily on Days 1 – 4 during Week 2, and the Week 2 results will be used to make decisions about the Week 3 dose. If a subject still does not meet the twice weekly criteria when dosed at 200 mg/m^2 once weekly, discontinue the subject and replace. After both the brequinar PK and 72h DHO level meet criteria described in the Individual Dose Adjustment Guidelines (below), the subject may move to twice-weekly dosing on a continuing basis as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria also described in the Guidelines for Individual Dose Adjustment. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.
Primary endpoints:	● Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	● Rates of treatment-emergent adverse events. ● Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. ● Event free survival (EFS). ● Duration of response. ● PK profile of brequinar.

	● DHO plasma profile.
Exploratory endpoints:	● 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
Sample Size:	Up to 27 subjects
Number of Sites:	3 – 6
Study Period:	An enrollment period of 18 - 24 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial. 2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL) and who have exhausted available therapy. 3. ECOG Performance Status 0 to 2. 4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2. 5. Adequate hepatic function (unless deemed to be related to underlying leukemia). 1. Direct bilirubin $\leq$ 2 x ULN 2. ALT $\leq$ 3 x ULN 3. AST $\leq$ 3 x ULN 6. Adequate renal function as documented by creatinine clearance $\geq$ 30 mL/min based on the Cockcroft-Gault equation. 7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time. 8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating

	physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration. 9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.
Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 3. QTc interval using Fridericia's formula (QTcF) $\geq$ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor. 4. Pre-existing liver disease. 5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of $\geq$ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 7. Active cerebrospinal involvement of AML, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL). 8. Diagnosis of acute promyelocytic leukemia (APL) 9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 12. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
Treatment	This is an open-label study of dose-adjusted brequinar for the treatment of AML and other hematologic malignancies. Brequinar is supplied as 100 mg or 250 mg

	oral capsules which will be used to dose subjects on a mg/m^2 basis as described in the Guidelines for Individual Dose Adjustment section below.
Procedures	**Screening Visit (Study Days -14 to -1)** These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: • Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study. • Pertinent medical/surgical history (including AML/other hematologic malignancy diagnosis and laboratory and clinical evidence of progression, previous AML/other hematologic malignancy treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications. • Physical examination (including weight). • Vital signs (heart rate, respiratory rate, blood pressure, body temperature). • Pregnancy test for women of childbearing potential (WOCBP). • ECOG performance assessment. • Hematology/chemistry. • 12-lead ECG with QTcF. • Standard chromosomal and mutational testing per institutional guidelines. • Bone marrow sampling • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available. **Dose Adjustment: Cycle 1 Week 1 (or Week 2)** **Week 1 (or Week 2) Day 1**: • Collect any adverse events or new concomitant medications since Screening. • Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. • Conduct physical examination (including weight) if >4 weeks since last performed, vital signs, pregnancy test for WOCBP if >4 weeks since last test, and 12-lead ECG if >4 weeks since last test. • Review results and confirm subject remains eligible for the study. • Dispense study medication.

	• Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose. • Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. • This week's procedures may be repeated for Week 2 if necessary, with the exception that PK/DHO samples are to be obtained only pre-dose on Day 1 of Week 2. **Week 1 (or Week 2) Day 2**: Collect 24h post dose brequinar/DHO and flow cytometry samples. **Week 1 (or Week 2) Day 3**: Collect 48h post dose brequinar/DHO and flow cytometry samples. **Week 1 (or Week 2) Day 4**: Collect 72h post dose brequinar/DHO and flow cytometry samples. **Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)** Once a subject reaches a twice-weekly dose, the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria. Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 from study Day 1 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only of each two-week cycle). **Maintenance Dose Cycle Day 1:** • Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit. • Collect pre-dose brequinar/DHO, hematology/chemistry, and flow cytometry sample. • Obtain vital signs; pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ± 7 days), at the Week 7 visit (Day 43 ± 7 days), then every 12 weeks ± 7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity. • If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL). • Dispense study medication. • Dispense calendar/diary.

	Maintenance Dose Cycle Day 8 (up to Week 12): • Collect pre-dose brequinar/DHO/flow cytometry sample. • Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL). **Final Visit** This visit is to take place when a subject is discontinuing from the study. • Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. • Collect brequinar/DHO/flow cytometry and hematology/chemistry samples. • Collect unused study medication. • Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed. • Ensure all adverse events have been recorded. **Telephone Follow Up Visit (2 weeks after Final Visit)** Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication). **Unscheduled Visits** Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.
Safety/ Tolerability	**Safety/Tolerability – Subject Level** Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting toxicity (DLT) during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in the table below. If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled assessments. If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

<table>
<tr>
<td></td>
<td>
Exceptions to Grade 3 Nonhematologic AEs
<table>
<tr><th>Condition</th><th>Exception Description</th></tr>
<tr><td>Nausea/ Emesis</td><td>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.</td></tr>
<tr><td>Diarrhea</td><td>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.</td></tr>
<tr><td>Laboratory abnormalities</td><td>Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.</td></tr>
<tr><td>Mucositis</td><td>Grade 3 with duration < 1 week</td></tr>
<tr><td>Fatigue</td><td>Grade 3 with duration < 2 weeks</td></tr>
</table>

For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

Hematologic Toxicity
After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.
</td>
</tr>
<tr>
<td>Cohort Starting Doses</td>
<td>Cohort 1 enrollment was stopped after treating 5 subjects at 500 mg/m^2 twice weekly to allow data review and analysis. No dose escalation was permitted for Cohort 1 subjects. Due to extensive study design changes a sixth subject will not be enrolled into Cohort 1. Cohort 2 treated 6 subjects with this starting dose once-weekly, which was adjusted to twice-weekly with an adjusted dose (if needed) based on brequinar PK and DHO levels.

Cohort 2 replacement subjects will begin with one dose of 350 mg/m^2. If the Week 1 brequinar PK and DHO levels meet the criteria to move to twice weekly dosing the subject will be dosed in Week 2 with 350 mg/m^2 twice weekly. If the subject does not meet the criteria to move to twice-weekly dosing in Week 1 (i.e., 48h BRQ PK > 5 mcg/mL and/or 72h DHO > 48h or 72h DHO ≥ 5,000 ng/mL),</td>
</tr>
</table>

	decrease the dose to 200 mg/m^2 for Week 2 and administer one dose. If the subject then meets twice weekly criteria, move to twice weekly dosing with 200 mg/m^2 beginning in Week 3. If the subject does not meet criteria to move to twice weekly dosing with the 200 mg/m^2 single dose, discontinue the subject. Each subject's dosing frequency and dose may be adjusted as shown below.
Expansion Cohort	An expansion cohort of up to 6 to 12 subjects will be added to obtain further information on safety, brequinar exposure, and DHO levels.
Guidelines for Individual Dose Adjustment	Cohort 1 is now complete; all subjects were dosed with 500 mg/m^2 twice weekly. The six initial Cohort 2 subjects had a starting dose of 500 mg/m^2 and were to take oral brequinar once weekly for at least two weeks (two total doses). Brequinar pharmacokinetics (BRQ PK) and dihydroorotate (DHO) levels from each week were used to determine the next week's dose. Additional weeks of once-weekly dosing were permitted as needed to adjust the dose until the criteria have been met or the dosing limits have been reached (minimum 200 mg/m^2, maximum 800 mg/m^2). In order to move to twice-weekly dosing as quickly as possible, the replacement Cohort 2 subjects will start with a once weekly dose of brequinar of 350 mg/m^2. If the subject meets twice weekly dosing criteria with this dose, move the subject move to twice weekly dosing with 350 mg/m^2 in Week 2. If the twice weekly criteria are not met in Week 1, decrease the dose for Week 2 to 200 mg/m^2 and dose once. If the subject now meets dosing criteria with 200 mg/m^2, begin twice weekly dosing with 200 mg/m^2 in Week3. If the twice weekly dosing criteria are not met with 200 mg/m^2, discontinue this subject. Subjects who meet twice weekly dosing criteria will dose twice weekly (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis. After beginning twice weekly dosing, the brequinar dose is to be further adjusted when necessary using the DHO level obtained approximately 84 hours after a twice-weekly dose (84h DHO). For example, a subject dosing twice weekly on Monday mornings and Thursday evenings would dose on a Thursday evening and the 84h DHO sample would be obtained the following Monday morning. There is no upper or lower dose limit during twice weekly dosing. Dose increases and continued dosing must first meet acceptable safety requirements. If unacceptable safety occurs, hold dosing until AE resolves to ≤ grade 2, reduce dose by 150 mg/m^2 and resume dosing. Discontinue the subject if a dose reduction leads to a dose of zero or if the available capsule strengths cannot accommodate the desired mg/m^2 dose. If brequinar PK or DHO levels are not available for dose adjustment decisions, hold dosing until results are available.

Algorithm to Set Twice-Weekly Brequinar Dose for Cohort 2 Replacements/Expansion Cohort (Starting Dose 350 mg/m^2)

48h BRQ PK > 5 mcg/mL	NA	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 2 or after

* Brequinar PK (BRQ PK) Criteria for Cohort 2 replacements and Expansion Cohort: 48h BRQ ≤
**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL

After the twice-weekly dose has been determined using the above criteria, the twice-weekly dose may be further adjusted using the 84h DHO (trough) algorithm shown below. The 84h DHO level obtained at the beginning of each week will be used to adjust the next week's dose as needed. This dose adjustment may be made each week through Week 12 and every two weeks after Week 12, if necessary.

Algorithm to Adjust Twice-Weekly Dose using 84h DHO for Cohort 2 Replacements and Expansion Cohort

84h DHO (Trough)	**Action**
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly through Week 12 then every 2 weeks. Adjust dose prn per 84h DHO criteria.
84h DHO ≥ 5000 ng/mL	HOLD. Notify subject not to take next dose. Hold dosing for one week. If next Day 1 84h DHO is < 5,000 ng/mL, decrease next dose by 75 mg/m^2 and resume twice-weekly dosing. If next Day 1 84h DHO ≥ 5,000 ng/mL, no further dosing, discontinue the subject.

Each subject will continue twice-weekly dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels. Subjects who discontinue for any reason prior to the Day 43 visit may be replaced.
The dose adjustment procedures may be revised after safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed.

Brequinar/DHO	Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule: • Cycle 1 Week 1 (and Week 2 if weekly dose decreased): Day 1 (prior to dosing, and 1, 2, 4, and 6 hours), Days 2, 3, and 4 (24h, 48h, and 72h after dosing) • After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12, then every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle). • Final Visit: obtain brequinar, DHO, and flow cytometry samples.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP. Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR

	• Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR • Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.

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3 INTRODUCTION

3.1 BACKGROUND

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML and many other hematologic malignancies remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10% (SEER, 2015 [1]). It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

3.2 DIHYDROOROTATE DEHYDROGENASE (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous, essential enzyme. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect

of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

Activated and proliferating T-cells have a particular dependence on nucleotide synthesis and nucleotide pools (Cohen et al., 1983 [15], Quéméneur et al., 2003 [16]), thus additional leukemias that may also benefit from brequinar's mechanism of action include T-cell lymphoblastic leukemia (T-ALL), bi-lineal leukemia (BLL), and mixed phenotypic acute leukemia (MPAL).

3.3 BREQUINAR

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. (Sykes et al., 2016 [4]) showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based

on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

3.4 RATIONALE FOR THE PLANNED TRIAL

This study is designed to obtain safety and efficacy data for brequinar in patients with AML and other hematologic malignancies including T-ALL, BLL, and MPAL as these diseases may benefit from brequinar.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification and other hematologic malignancies including T-ALL, BLL, and MPAL that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The dose-adjustment scheme is presented in detail in Section 8.5.

3.4.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-weekly administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a twice-weekly schedule of brequinar dosed approximately every 84 hours, while measuring brequinar PK and plasma DHO to fine-tune the dose that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see Brequinar IB, Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggested that a starting dose for Cohort 1 of 500 mg/m^2 p.o. would be safe and well-tolerated in subjects with AML. This 500 mg/m^2 starting dose was used in Cohorts 1 and 2 in this protocol, however Cohorts 1 and 2 results indicate that a starting dose of 350 mg/m^2 should allow subjects to more rapidly progress to twice weekly dosing. The starting brequinar dose for the remainder of Cohort 2 will therefore be reduced to 350 mg/m^2. Each subject's subsequent brequinar dosing may be adjusted depending

on the safety, tolerability, brequinar PK, and DHO level obtained during the period following dose adjustment. See Section 8.4.

3.5 RISK/BENEFIT OF BREQUINAR

As presented in the brequinar IB, more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of leukemia is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with hematologic malignancies typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

3.6 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

In studies utilizing the weekly schedule of administration of brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the guidelines presented in Section 10.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and treatment are described in Sections 10.10 and 10.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 10.7.

3.7 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar Investigator's Brochure [9]; nonclinical data on file with Clear Creek).

3.8 STEPS TO BE TAKEN TO CONTROL OR MITIGATE RISKS

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 10. All subjects will be treated by highly experience hematologic oncologists familiar with the treatment of pancytopenia and its side effects.

4 TRIAL OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine the safety and tolerability of brequinar and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML and other hematologic malignancies.

4.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

4.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

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

5 TRIAL DESIGN

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 and other hematologic malignancies. The study will also assess the inhibition of DHODH and the PK profile of brequinar in plasma. Intra-subject dosing may be adjusted based on safety/tolerability, brequinar pharmacokinetics (PK), and DHO levels.

Up to 27 subjects are planned to be entered in this trial. Although Cohort 1 was planned to have 6 subjects, enrollment in this cohort was stopped after 5 subjects when brequinar PK and DHO results became available; these results led to changes in study design utilized in Cohort 2. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly.

Although the 500 mg/m^2 starting dose of brequinar was well tolerated by some subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses lower than 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, newly enrolled Cohort 2 subjects will now start with 350 mg/m^2 once weekly. Approximately 3 additional subjects will be enrolled into Cohort 2 and may be followed by an expansion cohort of approximately 6-12 subjects. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 dose and schedule. Subjects who meet the twice weekly brequinar PK and 72h DHO criteria in Week 1 may proceed to twice weekly dosing with 350 mg/m^2 in Week 2. Subjects whose brequinar PK and DHO levels do not meet the twice weekly criteria will have the dose decreased to 200 mg/m^2 once weekly. For subjects requiring the dose decrease, brequinar PK and DHO samples will also be obtained once daily on Days 1 – 4 during Week 2, and the Week 2 results will be used to make decisions about the Week 3 dose. If a subject still does not meet the twice weekly criteria when dosed at 200 mg/m^2 once weekly, discontinue the subject and replace if agreed by the sponsor.

After both the brequinar PK and 72h DHO level meet criteria described in Section 8.5.1, the subject may move to twice-weekly dosing as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria described in Section 8.5.2. There is no upper or lower limit for brequinar dose during twice weekly dosing.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression.

Study procedures are presented in detail in Section 8.

6 TRIAL ENDPOINTS

6.1 PRIMARY ENDPOINT

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

6.2 SECONDARY ENDPOINTS

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

6.3 EXPLORATORY ENDPOINTS

- 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

7 TRIAL POPULATION

7.1 NUMBER OF SUBJECTS

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

7.2 INCLUSION CRITERIA

1. Willing and able to provide written informed consent for the trial.

2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL) and who have exhausted available therapy.

3. ECOG Performance Status 0 to 2.

4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2.

5. Adequate hepatic function (unless deemed to be related to underlying leukemia).

    a. Direct bilirubin $\leq$ 2 x ULN

    b. ALT $\leq$ 3 x ULN

    c. AST $\leq$ 3 x ULN

6. Adequate renal function as documented by creatinine clearance $\geq$ 30 mL/min based on the Cockcroft-Gault equation.

7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time.

8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.

9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

7.3 EXCLUSION CRITERIA

1. Patients in need of immediate leukapheresis.

2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.

3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.

4. Pre-existing liver disease.

5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.

6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).

7. Active cerebrospinal involvement of AML, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL).

8. Diagnosis of acute promyelocytic leukemia (APL).

9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.

10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.

11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.

12. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.

7.4 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

Up to 27 subjects are planned to be entered in this trial. Although Cohort 1 was planned to have 6 subjects, enrollment in this cohort was stopped after 5 subjects when brequinar PK and DHO results became available; these results led to changes in study design as described in this section. The sixth subject was not be enrolled in Cohort 1. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly. Although the 500 mg/m^2 starting dose of brequinar was well tolerated by some subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses below 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, newly enrolled (replacement) Cohort 2 subjects will start with 350 mg/m^2 once weekly. Cohort 2 will enroll approximately 3 additional subjects at this starting dose and may be followed by an expansion cohort of approximately 6 to 12 subjects.

After both the brequinar PK and 72h DHO level meet criteria described in Section 8.5.1, the subject may move to twice-weekly dosing as tolerated. The twice-weekly dose may be further adjusted using 84h DHO (trough ~84 hours after dosing) criteria described in Section 8.5.2.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters.

Dosing will continue for 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.

8.1 DESCRIPTION OF BREQUINAR

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis and will be adjusted based on tolerability, safety, brequinar PK, and DHO levels. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 24 hours. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

8.2 TREATMENT ADMINISTRATION

Five subjects were enrolled in the now-completed Cohort 1. All subjects were dosed with twice weekly brequinar 500 mg/m^2 for a range of 2 to 16 doses (one to 8 weeks). No additional subjects will be enrolled into Cohort 1. A total of 6 subjects were treated in Cohort 2 with a starting dose of 500 mg/m^2 once weekly. These 6 Cohort 2 subjects took brequinar once weekly for at least two weeks (two total doses). Brequinar exposure and DHO levels were used to adjust the brequinar

dose (if necessary) to meet brequinar PK and 72h DHO criteria described in Section 8.5.1. Subjects then moved to twice-weekly dosing (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis. The brequinar dose was further adjusted if needed using the 84h DHO (trough) Criteria shown in Section 8.5.2.

Three Cohort 2 were not evaluable due to early discontinuation. Approximately 3 additional subjects will be enrolled into Cohort 2 to replace these subjects and may be followed by an expansion cohort of approximately 6-12 subjects. Cohort 2 subjects will now start with 350 mg/m^2 once weekly. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 dose and schedule. Subjects who meet the twice weekly brequinar PK and 72h DHO criteria in Week 1 may proceed to twice weekly dosing with 350 mg/m^2 in Week 2. For subjects whose brequinar PK and DHO levels do not meet the twice weekly criteria, decrease the dose to 200 mg/m^2 once weekly. For these subjects, brequinar PK and DHO samples will also be obtained once daily on Days 1 – 4 during Week 2, and the Week 2 results will be used to make decisions about Week 3. If a subject still does not meet the twice weekly criteria when dosed at 200 mg/m^2 once weekly, discontinue the subject. Subjects who discontinue for any reason prior to 6 weeks may be replaced with sponsor permission.

Each dose is to be taken with approximately 240 mL of water. The subject does not need to be fasting. Each dose will generally consist of multiple capsules; the capsules do not need to be swallowed all at once but can be spread over up to 15 minutes as needed. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar/DHO samples and results needed for dosing adjustments. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

8.3 SAFETY/TOLERABILITY

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Cohort 1 had a fixed starting dose of 500 mg/m^2 with no dose escalation permitted. Cohort 2 and the expansion cohort started with 500 mg/m^2 once weekly and had adjustments made to dose and dose frequency using safety/tolerability, brequinar exposure (PK), and DHO levels. As described above, the replacement Cohort 2 subjects (and the Expansion Cohort) will start at 350 mg/m^2 once weekly with the goal of moving rapidly to twice weekly dosing. Safety at the subject level is defined in Section 8.3.1; hematologic toxicity is defined in Section 8.3.2.

The following adverse events are commonly observed in patients with hematologic malignancies and should be differentiated from possible adverse effects of brequinar: fatigue, fever, thrombocytopenia and other cytopenias, infection, pallor, shortness of breath, weight loss, night sweats, and anorexia. Any of these events can be serious in nature and may result in death. Disease progression is considered a lack of efficacy rather than an adverse event. Death from disease progression is to be reported as presented in Section 10.

Adverse events commonly observed in patients treated with brequinar are provided in the Investigator's Brochure and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 subjects treated once-weekly (DuP 785-012), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In most instances, drug related toxicities were clinically manageable and reversible upon discontinuation of brequinar treatment. In a study where brequinar was dosed twice-weekly to solid tumor subjects, no drug-related deaths occurred. Stomatitis/mucositis was observed in 13 of the 19 (68%) patients across all doses. Mild to moderate (Grades 1 and 2) stomatitis was observed in 10 patients with a more severe (Grade 3) stomatitis seen in 3 patients at doses over 600 mg/m^2. One patient at 600 mg/m^2 had drug discontinuation due to drug-related stomatitis. Myelosuppression was the main dose-limiting toxicity (DLT) with thrombocytopenia (Grades 1-4), observed after 2 to 9 doses above 600 mg/m^2. Any of these events reported with brequinar use can be serious in nature and may result in death.

Prescriptions can be provided in advance for supportive care for common brequinar-related AEs such as mucositis.

8.3.1 Safety/Tolerability – Subject Level

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML and other hematologic malignancies, hematologic AEs of any grade will not be considered a DLT during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in Table 8-1.

If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled visits and assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Table 8-1. Exceptions to Grade 3 Nonhematologic AEs

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 completion of the first 42 days of treatment, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for at least one week (i.e., two doses if twice weekly) for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

8.3.2 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit.

8.4 COHORT STARTING DOSES

Cohort 1 enrollment was stopped after treating 5 subjects at 500 mg/m^2 twice weekly to allow data review and analysis. No dose escalation was permitted for Cohort 1 subjects. Due to extensive study design changes a sixth subject will not be enrolled into Cohort 1.

The first 6 Cohort 2 subjects had a starting dose of 500 mg/m^2 once-weekly which was adjusted to twice-weekly with an adjusted dose (if needed) based on brequinar PK and DHO levels.

Cohort 2 replacement subjects will begin with one dose of 350 mg/m^2. If the Week 1 brequinar PK and DHO levels meet the criteria to move to twice weekly dosing the subject will be dosed in Week 2 with 350 mg/m^2 twice weekly. If the subject does not meet the criteria to move to twice-

weekly dosing in Week 1 (i.e., 48h BRQ PK > 5 mg/mL and/or 72h DHO > 48h or 72h DHO ≥ 5,000 ng/mL), decrease the dose to 200 mg/m^2 for Week 2 and administer one dose. If the subject then meets twice weekly criteria, move to twice weekly dosing with 200 mg/m^2 beginning in Week 3. If the subject does not meet criteria to move to twice weekly dosing with the 200 mg/m^2 single dose, discontinue the subject.

Each subject's dosing frequency and dose may be adjusted as shown in the following sections.

8.5 INDIVIDUAL DOSE ADJUSTMENT GUIDELINES

Cohort 1 is now complete; all subjects were dosed with 500 mg/m^2 twice weekly.

The six initial Cohort 2 subjects had a starting dose of 500 mg/m^2 and were to take oral brequinar once weekly for at least two weeks (two total doses). Brequinar pharmacokinetics (BRQ PK) and dihydroorotate (DHO) levels from each week were used to determine the next week's dose. Additional weeks of once-weekly dosing were permitted as needed to adjust the dose until the criteria have been met or the dosing limits have been reached (minimum 200 mg/m^2, maximum 800 mg/m^2).

Pre-clinical evidence (Sykes et al., 2016 [4]) suggests that a twice-weekly dose is most likely to lead to efficacy, therefore the goal is to adjust the brequinar dose to allow all subjects to dose on a twice-weekly basis. In order to move to twice-weekly dosing as quickly as possible, the replacement Cohort 2 subjects will start with a once weekly dose of brequinar of 350 mg/m^2. If the subject meets twice weekly dosing criteria with this dose, move the subject move to twice weekly dosing with 350 mg/m^2 in Week 2. If the twice weekly criteria are not met in Week 1, decrease the dose for Week 2 to 200 mg/m^2 and dose once. If the subject now meets dosing criteria with 200 mg/m^2, begin twice weekly dosing with 200 mg/m^2 in week 3. If the twice weekly dosing criteria are not met with 200 mg/m^2, discontinue this subject. Subjects who meet twice weekly dosing criteria will dose twice weekly (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis.

After beginning twice weekly dosing, the brequinar dose is to be further adjusted when necessary using the DHO level obtained approximately 84 hours after a twice-weekly dose (84h DHO). For example, a subject dosing twice weekly on Monday mornings and Thursday evenings would dose on a Thursday evening and the 84h DHO sample would be obtained the following Monday morning. There is no upper or lower dose limit during twice weekly dosing.

Dose increases and continued dosing must first meet acceptable safety requirements as described in Section 8.3.1. If unacceptable safety occurs, hold dosing until AE resolves to ≤ grade 2, reduce dose by 150 mg/m^2 and resume dosing. Discontinue the subject if a dose reduction leads to a dose of zero or the available capsule strengths cannot accommodate the designed mg/m^2 dose. If brequinar PK or DHO levels are not available for dose adjustment decisions, hold dosing until results are available.

The dose adjustment procedures and criteria may be revised after each preceding cohort's safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed. The dose adjustment process and criteria are described in the following sections.

8.5.1 Brequinar Exposure (BRQ PK) and 72h DHO Criteria to Set Twice-Weekly Dosing

Both brequinar exposure (pharmacokinetics, PK) and dihydroorotate (DHO) levels are utilized to set the twice weekly dose. For Cohort 3, the initial goal is to identify a dose that results in brequinar PK approximately 48 hours after dosing of less than or equal to 5 mcg/mL (48h BRQ PK ≤ 5 mcg/mL). Next check the DHO results obtained 48 and 72 hours after dosing. The twice weekly DHO criteria are that the DHO obtained 72 hours after dosing must be less than the DHO obtained 48 hours after dosing (i.e., on a downward slope). In addition, the DHO level at 72 hours must be less than 5,000 ng/mL. To summarize, 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL. See the algorithm to set the twice weekly dose for Cohort 3 in Table 8-2 and Figure 8-1.

Table 8-2. Algorithm to Set Twice-Weekly Dose for Cohort 2 Replacement/Expansion Subjects (Starting Dose 350 mg/m^2)

Brequinar PK*	72h DHO**	Action
48h BRQ PK > 5 mcg/mL	NA	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 2 or after

* Brequinar PK (BRQ PK) Criteria for Cohort replacements and Expansion Cohort: 48h BRQ ≤ 5 mcg/mL

**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL

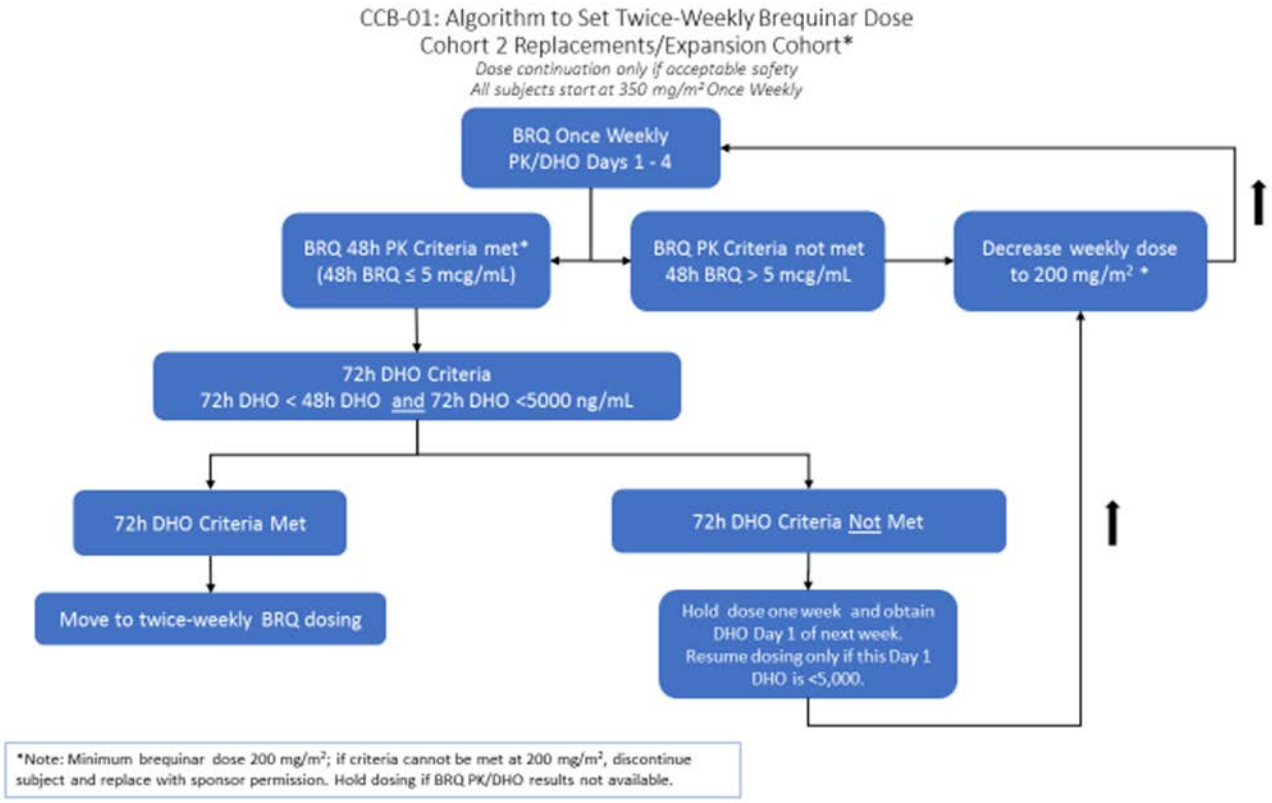

Figure 8-1. Algorithm to Set Twice-Weekly Dose

8.5.2 Dose Adjustment Using 84h DHO

After the twice-weekly dose has been determined using the above criteria and the subject has started to dose twice weekly, the twice-weekly dose may be further adjusted using the 84h DHO algorithm shown below. The 84h DHO level obtained prior to the first dose of a week will be used to adjust the next week's dose as needed. This dose adjustment may be made on a continuing basis. If DHO levels are not available for dose adjustment decisions, confirm safety is acceptable but hold the dose until results are available. As soon as results are available, adjust dose as needed following criteria and resume dosing. Further adjustments are permitted using the 84h DHO results during twice weekly dosing. There is no maximum or minimum allowable dose during twice weekly dosing. See Table 8-3 and Figure 8-2.

Table 8-3. Algorithm to Adjust Twice-Weekly Dose using 84h DHO for Cohort 2 Replacements and Expansion Cohort

84h DHO Criteria	Action
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly x 12 weeks then every 2 weeks. Adjust dose PRN per 84h DHO criteria.
84h DHO ≥ 5000 ng/mL	HOLD. Notify subject not to take next dose. Hold dosing for one week. If next Day 1 84h DHO is < 5,000 ng/mL, decrease next dose by 75 mg/m^2 and resume twice-weekly dosing. If next Day 1 84h DHO ≥ 5,000 ng/mL, no further dosing, discontinue the subject.

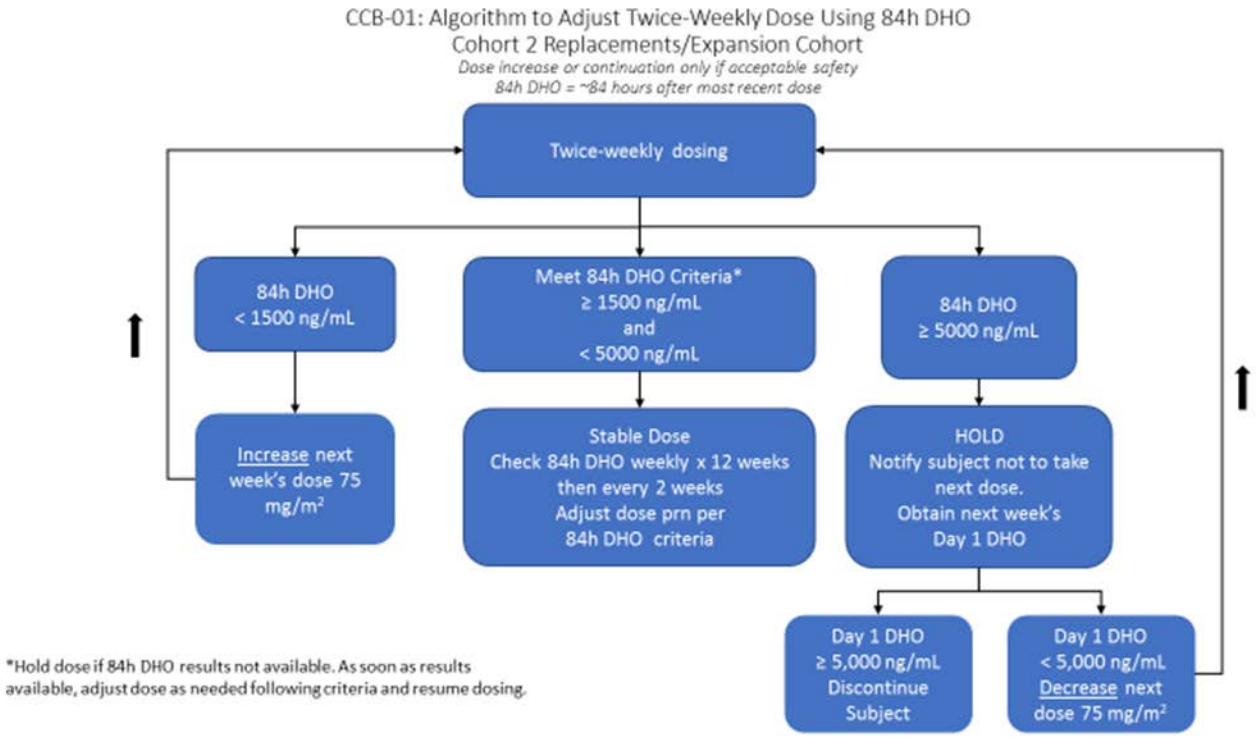

Figure 8-2. Algorithm to Adjust Dose Using 84h DHO

Each subject will continue twice-weekly dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels. Subjects who discontinue for any reason prior to the Week 7 (Day 43) visit may be replaced.

8.6 MEDICATION/AE DIARY

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

8.7 BONE MARROW BIOPSY

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the Week 4 visit (Day 22 ± 7 days), and one at the Week 7 visit (Day 43 ± 7 days); thereafter, bone marrow sampling will be obtained every 12 weeks ± 7 days (or per institutional standard of care) and at the Final Visit. If a participant develops frank evidence of progression of disease during the course of treatment based on laboratory or clinical assessment, he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at Visit 7 (Day 43) (defined as 43 days after initiating treatment or after 6 complete weeks after initiating study drug treatment regardless of number of doses), then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for any visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

8.8 EXPANSION COHORT

Following completion of Cohort 2, an expansion cohort of up to 6 to 12 subjects may be added to further define the dosing, BRQ PK and DHO criteria and assess the safety, tolerability, and biological activity of the dosing scheme.

The expansion cohort will follow the same visit procedures as Cohort 2.

8.9 STUDY DRUG DISCONTINUATION

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh) at or prior to Visit 7 (43 days) or with the agreement of the principle investigator and sponsor, the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued for an individual subject if there is evidence of unacceptable safety/tolerability that does not resolve to ≤ Grade 2 within 2 weeks after stopping brequinar dosing.

After treatment discontinuation, participants will be monitored for a minimum of 14 days after the last dose of brequinar or until they receive another treatment for their AML or other hematologic malignancy. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

8.10 BREQUINAR PHARMACOKINETICS (PK)/DIHYDROOROTATE (DHO) PLASMA LEVELS/FLOW CYTOMETRY

Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule and as shown in Section 15.3:

- Cycle 1 Week 1: Day 1 (prior to dosing, and 1, 2, 4, and 6 hours after dosing), Days 2, 3, and 4 (approximately 24h, 48h, and 72h after dosing)
- Cycle 1 Week 2 (if needed due to dose reduction): Day 1 prior to dosing, Days 2, 3, and 4 (approximately 24h, 48h, and 72h after dosing).
- After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12 from initial dose, then once every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle).
- Final Visit: obtain brequinar, DHO, and flow cytometry samples.

The samples will be processed and shipped per the instructions in the laboratory manual. If the samples are drawn on a weekend, holiday, or after hours, obtain the samples on the specified study day and ship the samples as soon as possible. Directions regarding sample processing and shipping are presented in a separate laboratory manual.

8.11 CONCOMITANT MEDICATION/TREATMENT

Record the name, start date, indication for use, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;

- Use of supportive care measures per institution’s standard of care are permitted at any time including hydroxyurea for the purpose of leukemic cytoreduction.

Transfusions are to be recorded beginning from up to 2 weeks prior to first dose of study drug and ongoing throughout the individual’s participation.

8.11.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended.

8.12 TREATMENT COMPLIANCE

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

8.13 STORAGE, STABILITY, LABELING AND PACKAGING

8.13.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.13.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-01
Contents: 100 or 250 mg Brequinar capsules
For oral use only. Take with approximately 8 ounces water every 3.5 days.
Subject Number: XX-XXXX
Treatment Duration: As directed
IND: 138355 Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.13.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist per the designated mg/m^2 dose for each subject. No randomization codes are necessary for this open-label study.

8.13.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the protocol and the Investigator's Brochure or are commonly associated with AML and other hematologic malignancies. The event will be considered expected if commonly associated with these diseases in the opinion of the investigator or Medical Monitor even if not specifically listed in these documents.

8.13.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

9 CONDUCT OF THE TRIAL

9.1 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

9.2 INFORMED CONSENT

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

9.3 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEES

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's Brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 SCHEDULE OF EVENTS

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the

Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), and lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential and platelet count, and peripheral blast count.

In addition to the already scheduled chemistry assessments, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.

9.5 STUDY CONDUCT

9.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study.
- Pertinent medical/surgical history (including AML/other hematologic malignancy diagnosis and laboratory and clinical evidence of progression, previous AML/other hematologic malignancy treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF.
- Standard chromosomal and mutational testing per institutional guidelines.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

9.5.2 Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available.

9.5.3 Dose Adjustment: Cycle 1 Week 1 (or Week 2 if dose reduced)

Week 1(or Week 2) Day 1

- Collect any adverse events or new concomitant medications since Screening.
- Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, pregnancy test for WOCBP if >4 weeks since last test and 12-lead ECG if >4 weeks since last test.
- Review results and confirm subject remains eligible for the study.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose during Week 1 only.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- This week's procedures may be repeated for Week 2 if necessary, with the exception that PK/DHO samples are to be obtained pre-dose only on Day 1 of Week 2 in addition to the daily samples on Days 2, 3, and 4.

Week 1 or 2 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples.

Week 1 or 2 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples.

Week 1 or 2 Day 4:

- Collect 72h post dose brequinar/DHO samples and flow cytometry samples.

9.5.4 Maintenance Dose Cycle

Once a subject reaches a twice-weekly dose (see Table 8-2 and Figure 8-2), the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria.

Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 from study Day 1 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only of each two-week cycle).

Maintenance Dose Cycle Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.

- Collect pre-dose brequinar/DHO, hematology/chemistry samples, and flow cytometry sample.

- Obtain vital signs; pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ±7 days), at the Week 7 visit (Day 43 ±7 days), then every 12 weeks ±7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity).

- If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).

- Dispense study medication.

- Dispense calendar/diary.

Maintenance Dose Cycle Day 8 (up to Week 12)

- Collect pre-dose brequinar/DHO, and flow cytometry sample.

- Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO <1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).

9.5.5 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.

- Collect brequinar/DHO/flow cytometry and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed.
- Ensure all adverse events have been recorded.

9.5.6 Telephone Follow Up Visit (2 weeks after Final Visit)

- Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

9.5.7 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.

9.6 COMPLIANCE WITH STUDY PROCEDURES

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified windows, it will not be necessary to file a protocol deviation.

9.7 EARLY WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;

- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

9.8 EARLY TERMINATION OF THE STUDY

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug, or until new treatment for AML/other hematologic malignancy is initiated, whichever occurs first.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug (e.g., discontinuation of study drug).

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the End of Study and Death forms.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. "Fatal" will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug.
    b. All serious adverse events regardless of attribution to the study drug.
    c. Any grade adverse event regardless of attribution to the study drug that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.

5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

(MD Anderson Cancer Center Leukemia-specific Adverse Event Recording and Reporting Guidelines)

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

10.1 CLASSIFICATION OF CAUSALITY

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, AML.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

10.2 CLASSIFICATION OF SEVERITY

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.3 SERIOUS ADVERSE EVENT (SAE) REPORTING

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only <u>one</u> event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

Death due to disease progression is considered to be an Expected event in these patients with relapsed/refractory AML/other hematologic malignancy and does not require reporting on an expedited basis.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING FAX: 919-313-1412 (US Toll-free: 1-866-761-1274)

SAE REPORTING EMAIL: safety-inbox.biotech@iqvia.com

MEDICAL MONITOR:	**Olga Prokopenko, MD (or other IQVIA Safety Monitor)**
E-mail:	olga.prokopenko@iqvia.com YYA36071medmon@iqvia.com
Telephone:	O: +49 610 25790871 M: +49 1522 8806304
24-hour safety line:	1-866-758-2798 or 919-313-7111
Fax:	206-826-0483

Sponsor Representative:	**Barbara Powers, MSN, Ph.D.**
E-mail:	bpowers@clearcreekbio.com
Telephone:	484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

10.5 PREGNANCIES

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported on a Pregnancy Form to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The pregnancy information should be submitted using a Pregnancy Report Form. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.6 HEMATOLOGIC ADVERSE EVENTS

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone

marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

10.7 MANAGEMENT OF MYELOSUPPRESSION

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML/other hematologic malignancy. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

10.8 DIFFERENTIATION SYNDROME

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
    - Control of leukocytosis with hydroxyurea;
    - Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs,

continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated once the participant's clinical condition improves, upon discussion with the Sponsor and Medical Monitor.

10.9 TUMOR LYSIS SYNDROME (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML/other hematologic malignancy for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC $< 25 \times 10^9$ /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100×10^9 /L or WBC $< 25 \times 10^9$ /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100×10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).

- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 10-1 provides a flow chart for TLS monitoring.

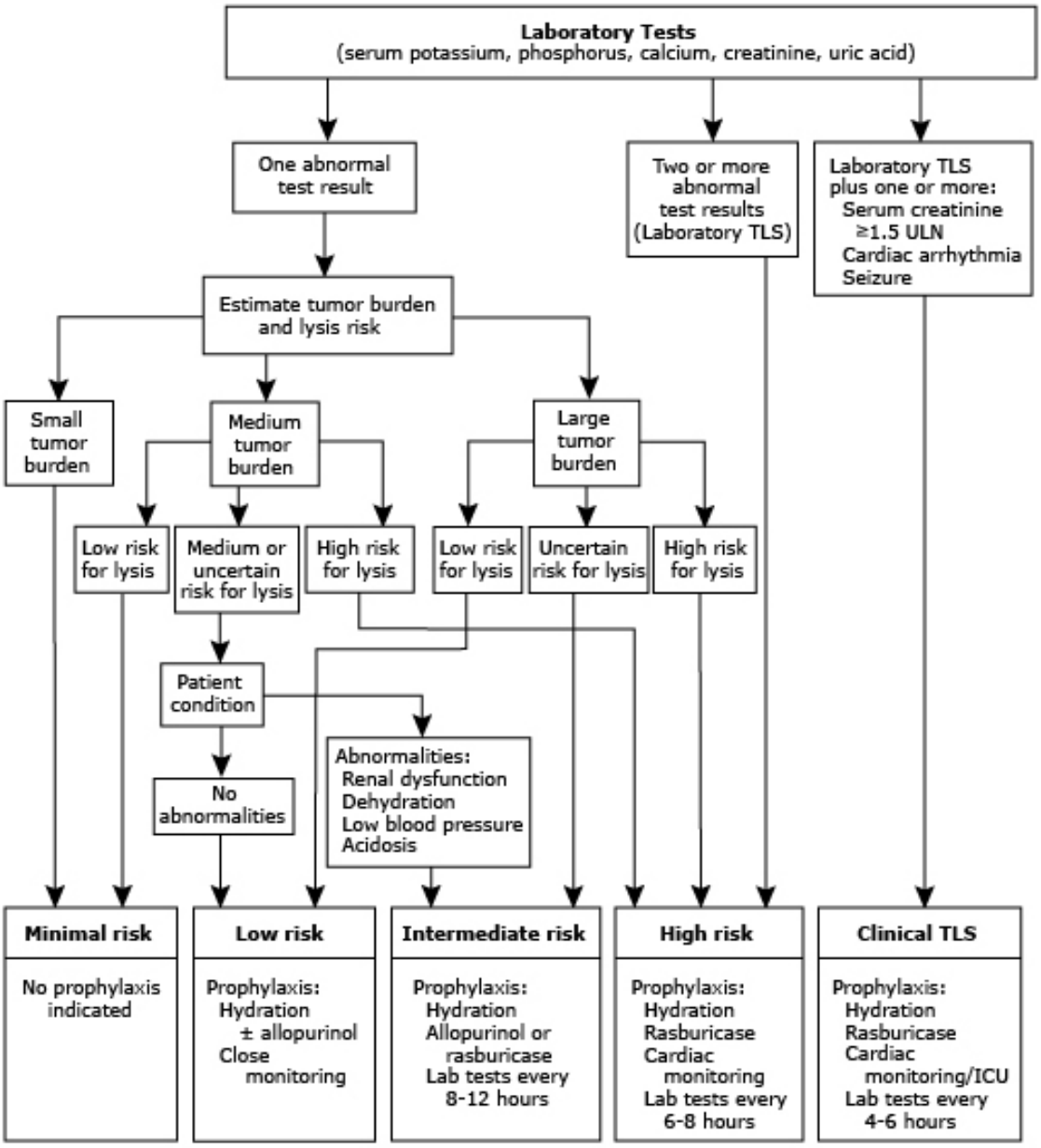

Figure 10-1. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

10.10 INFECTION PROPHYLAXIS

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

10.11 GROWTH FACTOR SUPPORT

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

10.12 MANAGEMENT OF NAUSEA, VOMITING, AND DIARRHEA

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 STUDY POPULATIONS FOR ANALYSIS

The analysis sets are defined in Table 11-1.

Table 11-1.Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML/other hematologic malignancy disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

11.2 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30

days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

11.3 EFFICACY ANALYSES

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 11-2 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 11-2.Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses may be performed for the above secondary endpoints from first dose

	of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML/other hematologic malignancy will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response

- Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.

- Platelet response
  - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

11.4 OTHER ENDPOINTS

Brequinar Pharmacokinetics (PK) and DHO Levels

Blood samples for brequinar PK and DHO analyses will be obtained at pre-specified times. The following plasma parameters may be analyzed (including but not limited to): concentration maximum (C_{max}), time of peak concentration (T_{max}) elimination half-life ($T_{1/2}$), and area under the concentration curve (AUC) estimated by compartmental and non-compartmental analysis (WinNonlin or similar). Additional parameters may be added as necessary.

Concentration data, PK and DHO parameters will be tabulated and summarized using descriptive statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

11.5 SAMPLE SIZE CONSIDERATIONS

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 will had up to 6 subjects; Cohort 2 will have approximately 6 subjects. An expansion cohort of approximately 15 subjects will be enrolled to further refine brequinar PK and DHO criteria and to further assess the safety, tolerability, and biological activity of this dosing scheme.

11.6 RANDOMIZATION

No randomization scheme is needed for this open label study.

11.7 POOLING OF STUDY CENTERS

Not applicable to this small, early phase study.

11.8 INTERIM ANALYSIS

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 INVESTIGATOR'S PERFORMANCE

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 15.7) to indicate commitment to comply with the contents.

12.2 CONFIDENTIALITY

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 SOURCE DOCUMENTATION

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;
- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 DATA COLLECTION

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

12.5 CASE REPORT FORMS, INVESTIGATOR'S SITE FILE AND RECORD RETENTION

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial

correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 NON-PROTOCOL RESEARCH

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 PUBLICATION

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 GENERAL

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

13.2 INDEMNITY

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 DATA MONITORING

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 AUDIT

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 CONFIDENTIALITY

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 FINANCE

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

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15 APPENDICES

15.1 APPENDIX A: CCB-01 SCHEDULE OF EVENTS

CCB-01 Schedule of Events **Procedures[a]**	**Screen[b]**	**Cycle 1 Week 1 or 2**		**Maintenance Dose Cycle**	**Final Visit**	**F/U Phone Call**	**Survival**
		D1	**D2 -D4**	**D1 & D8**		**Final Visit + 2 wks**	
Informed Consent[b]	X						
AE/Concomitant Medications	X	X	X	X	X	X	
Medical history[c]	X						
Demographics[d]	X						
Physical Exam[d]	X	X			X		
Vital Signs[d]	X	X		X	X		
Pregnancy Test (urine or serum)	X			X q 4 weeks	X		
ECOG Performance Status	X						
Hematology/Chemistry[e]	X	X		X (D1 only)	X		
Chromosomal/mutational testing[f]	X						
12-lead ECG	X			X q 4 weeks	X		
Bone Marrow Sampling[g, h]	X			X q 12 weeks	X		
Biobanking samples[g]	X			X	X		
Brequinar/DHO/Flow Cytometry Sample[h]		X	X	X	X		
Ship DHO Plasma Samples[i]			X (D4)	X	X		
Dispense/Collect Study Medication		X		X	X		
Dispense/Collect Subject Calendar/Diary		X		X	X		
Survival Assessment							X

a. Visit window of ± 1 day for Cycle 1 visits; window of ± 3 days for Maintenance Dose cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <1 week since Screening assessment. ECG and pregnancy test frequency are every 4 weeks or per institutional guidelines.
c. Medical history is to include AML/other hematologic malignancy diagnosis, previous AML/other hematologic malignancy treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Complete physical examination and vital signs once every 4 weeks or more often if needed to assess an AE.
e. If additional complete blood count (CBC) with differential results are available (for example, daily reports when a subject is hospitalized), these results may be captured in the eCRF using an Unscheduled visit.
f. Testing panel is per institutional standard of care; obtain sample at Screening.
g. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking for possible further analysis from Screening, Week 7 (Day 43), and Final Visit. Perform bone marrow sampling at screening, at Visit 4 (Day 22), Visit 7 (Day 43), then once every 12 weeks. Timing of this procedure may be adjusted to ensure results are available for the next clinic visit. Procedure window is ±7 days.
h. Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.
i. Process, store and ship these samples per the Laboratory Manual.
j. Cycle 1 Week 1 procedures are to be repeated for Week 2 if starting dose was decreased to 200 mg/m^2 or dose held until a twice-weekly dose has been determined with the exception that PK/DHO/Flow samples will be obtained only once per day in Week 2.

15.2 APPENDIX B: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15.3 APPENDIX C: BREQUINAR/DHO/FLOW CYTOMETRY SAMPLING

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.

Brequinar and DHO plasma samples and peripheral blood for flow cytometry are to be obtained at the following time points:

	Cycle 1 Week 1 (or 2)							
	D1					D2	D 3	D 4
Time Point	Pre-dose	1h*	2h*	4h*	6h*	24h	48h	72h
*These time points to be obtained in Week 1 only.								

	Maintenance Cycle **(Day 8 through Week 12 only)**	
	D1	D8
Time Point	Pre-dose ~84h after previous dose	Pre-dose ~84h after previous dose

15.4 APPENDIX D: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

15.5 APPENDIX E: SAMPLE SUBJECT CONSENT FORM

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 4.0 21 February 2020>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML/other hematologic malignancy may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML/other hematologic malignancy that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 - 12 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will begin the study by taking the study medication once a week for at least the first week. After the results of certain blood tests are known (level of study drug and the enzyme being tracked in this study), the dose may be adjusted and your schedule may be changed to twice-weekly or about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings for the remainder of the time you are participating in the study. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first dosing cycle.

Cycle 1 Week 1 (also Cycle 1 Week 2 if dose reduced after Week 1 dosing)

- **Week 1 (or Week 2) Day 1:**

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination (including weight) (unless within one week of Screening), vital signs, pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and choose to participate, you will be given study medication to take while at this clinic visit.
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Week 1 (or 2) Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 (or 2) Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 (or 2) Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.

Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)

Once you reach a twice-weekly dose, you will be in the Maintenance Dose Cycle.

In the first 12 weeks from starting study drug (after finding twice-weekly dosing), the Maintenance Dose Cycle procedures will occur every week on Day 1 and Day 8. After completing 12 weeks from starting study drug, you may come to the clinic for a Maintenance Dose Cycle visit once every 2 weeks (Day 1 only).

Maintenance Dose Cycle Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination every 4 weeks (including weight) (unless within one week of Screening), vital signs, pregnancy test for women able to bear children once every 4 weeks, a 12-lead ECG once every 4 weeks, and a bone marrow sample every 12 weeks.
- Take the first dose of the week at the clinic; if you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week; if beyond Week 12, adequate medication will be provided for the entire two-week cycle.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

Maintenance Dose Cycle Day 8:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, and flow cytometry.
- Take the first dose of the week at the clinic.
- If you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.
- You will not need to have this visit after Week 12.

Final Visit

This visit is to take place when you are leaving the study. You will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.

- Have a physical examination (including weight), vital signs, pregnancy test for women able to bear children if more than 4 weeks since the last test, 12-lead ECG if more than 4 weeks since the last test, and bone marrow sample if more than 4 weeks since the last test.
- Any leftover study medication will be collected.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications.

Telephone Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by telephone approximately two weeks after Final Visit to inquire if any new adverse events have occurred. Survival information will be collected while you are participating in the study (i.e., up to 2 weeks after last dose of study medication).

Unscheduled Visits

You may ask to come to the clinic when needed to be seen for unscheduled visits and tests to assess any new medical events providing the onset occurs within two (2) weeks after you have taken the final dose of study medication.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia/hemorrhage (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea

- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Infections
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

Some of these side effects were severe enough in patients treated with brequinar to require hospitalization or caused death. In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause a condition called differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML/other hematologic malignancy is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

The study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.

- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers

involved in this study. These people will use these records to review the study and to check the safety of the study.

- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.

- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.

- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating

AML/other hematologic malignancy or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

_____	_____	_____	_____
Printed Name of Subject	Signature of Subject	Date	**Time**
_____	_____	_____	_____
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

15.6 APPENDIX F: WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized

representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

15.7 APPENDIX G: INVESTIGATOR'S STATEMENT AND AGREEMENT

STUDY NUMBER: CCB-01

STUDY TITLE: 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)

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

Site Address:

_____

_____

_____

_____

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)

Study No: CCB-01

Version Date: 09 March 2020

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 138335

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ABBREVIATIONS

Abbreviation	Definition
µg	Microgram
5-FU	5-Fluorouracil
AUC	Area Under Curve
BID	Bis in die (two times a day)
BLL	Bi-lineal leukemia
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
CL	Clearance
Cl_R	Low Renal Clearance
Cl_T	Low Plasma Total Clearance
CRh	Partial hematological response
CRi	Incomplete hematological response
CT	Computerized Tomography
CYP	Cytochrome P450
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DLT(s)	Dose-Limiting Toxicity(ies)
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Median Effective Dose
EORTC	European Organisation for the Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
F	Bioavailability
FDA	United States Food and Drug Administration
g	Grams
GI	Gastrointestinal
G-R	Good Risk Patients
HPLC	High-Performance Liquid Chromatography
HIPAA	Health Insurance Privacy and Portability Act
Hr	Hour
IB	Investigator Brochure
IP	Intraperitoneal
IV	Intravenous
kg	Kilograms
l	Liters
$LD_{(10, 50, 90)}$	Lethal $Dose_{(10\%, 50\%, 90\%)}$
LLN	Lower limit of normal
LPS	Lipopolysaccharide
M	Molar

MPAL	Mixed phenotypic acute leukemia
Mg	Milligram
mL	Milliliters
$MLED_{10}$	Mouse Equivalent Lethal Dose for 10% of population
mM	Micromolar
Mm	Millimeters
MRD	Minimal Residual Disease
MRT	Long Median Residence Time
MS	Mucositis/stomatitis
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI	United States National Cancer Institute
NMR	Nuclear Magnetic Resonance Spectroscopy
NSC	National Service Center
ORR	Overall Response Rate
PK	Pharmacokinetic(s)
PO	Per Orem
P-R	Poor Risk Patients
PR	Partial Response
PS	Performance Status
Pts.	Patients
QTcF	Corrected QT interval by Fredericia
RDP2	Recommended Dose for Phase II
RNA	Ribonucleic Acid
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the means
SI	Simulation Index
SPC	Summary of Product Characteristics
t½	Half-Life
T-ALL	T-cell lymphoblastic leukemia
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
Vd	Volume of Distribution
Vd_{SS}	Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

2 SYNOPSIS

IND	138,335
Title	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)
Protocol	CCB-01
Investigational Medicinal Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules to be taken every 3.5 days with approximately 240 mL of water. Each subject's mg/m^2 dose will be calculated based on body surface area at study entry; actual dose will be rounded down to the nearest mg based on available oral capsule doses. The brequinar dose will be adjusted based on PK and DHO levels. Ribavirin is available as 200 mg capsules to be taken BID. Ribavirin is to be taken with food. Ribavirin dosing will start at a fixed dose of 1000 mg BID after twice weekly brequinar dosing has started. The ribavirin dose will be adjusted per the guidelines below.
Primary Objective	● To determine the safety and tolerability of brequinar alone and in combination with ribavirin and the DHODH inhibitory level of brequinar in adult patients with AML and other hematological malignancies.
Secondary Objectives	● To determine the overall response rate (ORR) including complete remission (CR), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR) (criteria as defined in the ELN Guidelines, Döhner et al., 2017 and Cheson et al., 1990) 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. ● To characterize the pharmacokinetic (PK) profile of brequinar ● To characterize the dihydroorotate (DHO) plasma levels of brequinar after oral dosing.
Exploratory Objectives	● To assess the relationship between DHODH inhibition and the efficacy and safety of brequinar alone and in combination with ribavirin. ● To evaluate molecular and cellular biomarkers that may be predictive of antitumor level and/or treatment resistance including cytogenetics, molecular profiling, and flow cytometry during and after treatment.

	● To evaluate global gene expression profiles, DNA methylation profiles, and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.
Design	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 alone and, beginning with Cohort 3, in combination with ribavirin in adult subjects with AML and other hematological malignancies. The study will also assess the inhibition of DHODH and the PK profile of brequinar in plasma. Subject dosing will be adjusted based on safety/tolerability, brequinar pharmacokinetics, and DHO levels. Up to 27 subjects are planned to be entered in this trial. Cohort 1 enrolled 5 subjects. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly. Three Cohort 2 subjects discontinued from the study prior to Day 43 and may be replaced. Although the 500 mg/m^2 starting dose of brequinar was well tolerated by most subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses lower than 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, any newly enrolled Cohort 2 subjects are to start with 350 mg/m^2 once weekly. Approximately 3 additional subjects may be enrolled into Cohort 2. If Cohort 3 regulatory approval is achieved prior to completing Cohort 2, it is not required to complete Cohort 2 before beginning enrollment into Cohort 3. Cohort 2 subjects who are active in the study at the time of regulatory approval may roll over into Cohort 3. Cohort 3 will enroll approximately 6 to 9 subjects and may be followed by an expansion cohort of approximately 6 to 12 subjects. Cohort 3 and the Expansion Cohort will use the 350 mg/m^2 starting dose. After both the brequinar 48h PK and 72h DHO level meet criteria described in the Individual Dose Adjustment Guidelines below, the subject is to move to twice weekly brequinar dosing on a continuing basis as tolerated. After moving to twice weekly brequinar dosing, the brequinar dose is to be reduced if needed per the algorithm below to achieve an 84h DHO of < 5000 ng/mL. After achieving a brequinar twice weekly dose that achieves 84h DHO < 5000 ng/mL, ribavirin dosing will begin at 1000 mg BID in combination with twice weekly brequinar. After initiating ribavirin dosing, the brequinar dose will continue to be adjusted using the dosing adjustment algorithm below. After brequinar has reached a stable dose, ribavirin will be increased 400 mg BID every 4 weeks to a maximum of 1800 mg BID. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow

	sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters. Haptoglobin levels will be tested as needed to assess hemolytic anemia. Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression. Subjects who discontinue for any reason prior to at least 4 weeks of the brequinar/ribavirin combination may be replaced.
Primary endpoints:	● Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels
Secondary endpoints:	● Rates of treatment-emergent adverse events. ● Overall Response Rate (ORR) including CR, CRi, CRh, MLFS, or PR. ● Event free survival (EFS). ● Duration of response. ● PK profile of brequinar. ● DHO plasma profile.
Exploratory endpoints:	● 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
Sample Size:	Up to 27 subjects
Number of Sites:	3 – 8
Study Period:	An enrollment period of 18 - 24 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial. 2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL) and who have exhausted available therapy.

	3. ECOG Performance Status 0 to 2. 4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2. 5. Adequate hepatic function (unless deemed to be related to underlying leukemia). 1. Direct bilirubin ≤ 2 x ULN 2. ALT ≤ 3 x ULN 3. AST ≤ 3 x ULN 6. Adequate renal function as documented by creatinine clearance ≥ 50 mL/min based on the Cockcroft-Gault equation. 7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time. 8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration. 9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.
Exclusion Criteria:	1. Patients in need of immediate leukapheresis. 2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment. 3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.

	4. Pre-existing liver disease. 5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions: a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia. 6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5 mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD). 7. Active cerebrospinal involvement of AML, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL). 8. Diagnosis of acute promyelocytic leukemia (APL) 9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection. 10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication. 11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, hormonal therapy has been initiated, or the malignancy has been surgically removed or treated with definitive radiotherapy. 12. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 13. Documented hemoglobinopathy.
Treatment	This is an open-label study of dose-adjusted brequinar for the treatment of AML and other hematologic malignancies. Brequinar is supplied as 100 mg or 250 mg oral capsules which will be used to dose subjects on a mg/m^2 basis as described in the Cohort Starting Dose and Guidelines for Individual Dose Adjustment sections below. Ribavirin is supplied as 200 mg capsules and will be added in fixed doses as a combination therapy as described below.
Procedures	**Screening Visit (Study Days -14 to -1)**

	These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information: • Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study. • Pertinent medical/surgical history (including AML/other hematologic malignancy diagnosis and laboratory and clinical evidence of progression, previous AML/other hematologic malignancy treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications. • Physical examination (including weight). • Vital signs (heart rate, respiratory rate, blood pressure, body temperature). • Pregnancy test for women of childbearing potential (WOCBP). • ECOG performance assessment. • Hematology/chemistry. • 12-lead ECG with QTcF. • Standard chromosomal and mutational testing per institutional guidelines. • Bone marrow sampling • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period begins with Cycle 1, Day 1 of the first dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available. **Dose Adjustment: Cycle 1 Week 1 (or Week 2)** **Week 1 (or Week 2) Day 1**: • Collect any adverse events or new concomitant medications since Screening.

	• Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry. • Conduct physical examination (including weight) if >4 weeks since last performed, vital signs, pregnancy test for WOCBP if >4 weeks since last test, and 12-lead ECG if >4 weeks since last test. • Review results and confirm subject remains eligible for the study. • Dispense study medication. • Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose. • Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications. • This week's procedures may be repeated for Week 2 if necessary, with the exception that PK/DHO samples are to be obtained only pre-dose on Day 1 of Week 2. **Week 1 (or Week 2) Day 2**: Collect 24h post dose brequinar/DHO and flow cytometry samples. **Week 1 (or Week 2) Day 3**: Collect 48h post dose brequinar/DHO and flow cytometry samples. **Week 1 (or Week 2) Day 4**: Collect 72h post dose brequinar/DHO and flow cytometry samples. **Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)** Once a subject reaches a twice-weekly dose, the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria. Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 from study Day 1 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only of each two-week cycle). **Maintenance Dose Cycle Day 1:** • Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.

	• Collect pre-dose brequinar/DHO, hematology/chemistry, and flow cytometry sample. • Obtain vital signs; pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ± 7 days), at the Week 7 visit (Day 43 ± 7 days), then every 12 weeks ± 7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity. • If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL). • Dispense study medication. • Dispense calendar/diary. **Maintenance Dose Cycle Day 8 (up to Week 12):** • Collect pre-dose brequinar/DHO/flow cytometry sample. • Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL). **Final Visit** This visit is to take place when a subject is discontinuing from the study. • Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit. • Collect brequinar/DHO/flow cytometry and hematology/chemistry samples. • Collect unused study medication. • Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed.

<table>
<tr><td></td><td>
Ensure all adverse events have been recorded.
Telephone Follow Up Visit (2 weeks after Final Visit)

Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.
</td></tr>
<tr><td>Safety/

Tolerability</td><td>
Safety/Tolerability – Subject Level

Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML, hematologic AEs of any grade will not be considered dose-limiting toxicity (DLT) during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in the table below.

If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Exceptions to Grade 3 Nonhematologic AEs
<table>
<tr><th>Condition</th><th>Exception Description</th></tr>
<tr><td>Nausea/

Emesis</td><td>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.</td></tr>
<tr><td>Diarrhea</td><td>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.</td></tr>
<tr><td>Laboratory abnormalities</td><td>Asymptomatic Grade 3 laboratory abnormalities that are not considered to be clinically significant.</td></tr>
<tr><td>Mucositis</td><td>Grade 3 with duration < 1 week</td></tr>
<tr><td>Fatigue</td><td>Grade 3 with duration < 2 weeks</td></tr>
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</table>

	For the expansion cohort, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject. **Hematologic Toxicity** After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit. Hemolytic anemia has been reported in approximately 13% of subjects taking ribavirin in combination with interferon alfa-2a for hepatitis C. Decrease in haptoglobin levels to below the lower limit of normal in a subject with previously normal range haptoglobin prior to beginning ribavirin dosing will trigger an investigation of possible hemolysis in subjects taking the brequinar/ribavirin combination, and may lead to a discontinuation of ribavirin after discussion with the PI, Sponsor and Medical Monitor.
Cohort Starting Doses	Cohort 1 treated 5 subjects at 500 mg/m^2 twice weekly. Cohort 2 treated 6 subjects with this starting dose once weekly. Three Cohort 2 subjects discontinued prior to Day 43 and may be replaced using a starting dose of 350 mg/m^2. Cohort 3 and Expansion cohort subjects will have a starting dose of 350 mg/m^2.
Expansion Cohort	An expansion cohort of approximately 6 to 12 subjects may be added after completing Cohort 3 to obtain further information on safety, brequinar exposure, DHO levels, and the efficacy and safety of the ribavirin and brequinar combination.
Guidelines for Brequinar Individual Dose Adjustment	Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 dose and schedule. Subjects who meet the twice weekly brequinar PK and 72h DHO criteria in Week 1 (see algorithm below) may proceed to twice weekly dosing with 350 mg/m^2 in Week 2. Subjects whose brequinar PK and DHO levels do not meet the twice weekly criteria at the 350 mg/m^2 dose or have unacceptable

safety at this dose will have their dose decreased to 200 mg/m^2 once weekly. For subjects requiring the dose decrease, brequinar PK and DHO samples will also be obtained daily on Days 1 – 4 during Week 2 (or when dosing resumes following an AE), and the Week 2 results will be used to make decisions about the Week 3 dose. If a subject still does not meet the twice weekly criteria or has unacceptable safety when dosed at 200 mg/m^2 once weekly, discontinue the subject.

If brequinar PK or DHO levels are not available for dose adjustment decisions, hold dosing until results are available.

Algorithm to Set Twice-Weekly Brequinar Dose for Cohort 3/Expansion Cohort (Starting Dose 350 mg/m^2)

Brequinar PK	DHO	Action
48h BRQ PK > 5 mcg/mL	NA	Decrease dose to 200 mg/m^2 and continu weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose to 200 mg/m^2 and continu weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 2 or afte

* Brequinar PK (BRQ PK) Criteria for Cohort 3 and Expansion Cohort: 48h BRQ ≤ 5 mcg/r
**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 r

After beginning twice weekly dosing, the brequinar dose is to be further reduced (if needed) to achieve an 84h DHO < 5000 ng/mL.

Ribavirin dosing will begin when brequinar twice weekly dosing results in an 84h DHO < 5000 ng/mL. See "Ribavirin Dosing" below for further instructions regarding ribavirin dosing.

After starting ribavirin dosing, the twice weekly brequinar dose is to be further adjusted using the 84h DHO (trough) algorithm shown below. There is no upper or lower brequinar dose limit after achieving twice weekly dosing and ribavirin dosing has started. The 84h DHO level obtained 84 hours after a brequinar dose will be used to adjust the next dose as needed. This brequinar dose adjustment may be made every two weeks, if necessary.

Algorithm to Adjust Twice-Weekly Dose using 84h DHO for Cohort 3 and Expansion Cohort

84h DHO (Trough)	**Action**
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly through Week 12 then every 2 weeks. Adjust dose prn per 84h DHO criteria.

<table>
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<table>
<tr><td>84h DHO ≥ 5000 ng/mL</td><td>HOLD. Notify subject not to take next dose. Hold dosing for one week. If next Day 1 84h DHO is < 5000 ng/mL, decrease dose by 75 mg/m^2 and resume twice-weekly dosing. If next Day 1 84h DHO ≥ 5000 ng/mL, no further dosing, discontinue the subject.</td></tr>
</table>

Each subject will continue twice weekly brequinar dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels.

The dose adjustment procedures may be revised after safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed.</td></tr>
<tr><td>Ribavirin Dosing</td><td>Beginning with Cohort 3 and the expansion cohort (and for ongoing Cohort 2 subjects who have rolled over into Cohort 3), ribavirin will be added beginning at 1000 mg BID following the initial brequinar only period described above. Ribavirin dosing will begin when brequinar dosing has moved to twice weekly and the twice weekly 84h DHO (DHO 84 hours after a twice weekly brequinar dose) is confirmed to be < 5000 ng/mL, expected to be a period of approximately 3 to 6 weeks. After reaching a stable brequinar dose as defined by the algorithm above, the ribavirin dose will be increased by 400 mg BID approximately every 4 weeks. The maximum ribavirin dose is 1800 mg BID.

If a ribavirin-related adverse event occurs, ribavirin is to be held for 2 weeks and restarted if the AE resolves to < Grade 2. If ribavirin dosing can be restarted, the ribavirin dose will be reduced by 400 mg BID.

Either brequinar or ribavirin may continue to be administered as a single agent if either study drug is discontinued due to unacceptable safety related to either agent. Cohort 2 subjects rolling over into Cohort 3 must meet the requirements for twice weekly dosing before beginning ribavirin dosing.</td></tr>
<tr><td>Brequinar/DHO</td><td>Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule:

• Cycle 1 Week 1 (and Week 2 if weekly dose decreased): Day 1 (prior to dosing, and 1, 2, 4, and 6 hours), Days 2, 3, and 4 (24h, 48h, and 72h after dosing)

• After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12, then every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle).</td></tr>
</table>

	• Final Visit: obtain brequinar, DHO, and flow cytometry samples.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP. Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher). Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling. Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics. Efficacy analysis is described below. Assess anti-leukemic activity by ELN Guidelines including CRh, as follows: • Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR • Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR

	• Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi • Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh • Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS • Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR • Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death • Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses will be from first dose of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP. In addition to the bone marrow and hematologic criteria above, the criteria used for treatment efficacy in T-ALL and other hematologic malignancies include that all previous extramedullary manifestations of disease must be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement).

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3 INTRODUCTION

3.1 BACKGROUND

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20000 people are diagnosed with AML per year in the United States (US) (SEER, 2015 [1]). The median age at diagnosis is 67 years.

Although there have been recent advances including midostaurin, enasidenib, CPX-351, gemtuzumab ozogomycin and venetoclax, outcomes for patients with AML and many other hematologic malignancies remain poor. With modern treatment regimens, expected complete remission (CR) rates are 60-70%, but long-term cure rates are 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10% (SEER, 2015 [1]). It is therefore critical to improve both the remission rate and the durability of remission in AML patients of all ages.

3.2 DIHYDROOROTATE DEHYDROGENASE (DHODH)

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. The enzyme is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a ubiquitous, essential enzyme. The Miller syndrome, a rare autosomal recessive disorder in which patients have inherited hypomorphic mutations in both alleles of DHODH, results in multi-organ dysfunction (Ng et al., 2010 [2]). Two weak inhibitors of human DHODH are approved for clinical use. Leflunomide, a pro-drug, is used in the treatment of patients with rheumatoid arthritis. Its active form, teriflunomide, is marketed for multiple sclerosis. Leflunomide is known to affect erythroid differentiation of K562 cells in vitro, via the depletion of uridine triphosphate (UTP) and cytidine triphosphate (CTP) ribonucleotides (Huang et al., 2002 [3]). Despite the connection between bone marrow level, blood cell differentiation and DHODH, leukemia models of leflunomide have not been very promising. Leukemic mice treated with leflunomide demonstrated no reduction in leukemic burden and experienced significant weight loss and lethargy.

Recent nonclinical studies have demonstrated that inhibition of DHODH can overcome myeloid differentiation arrest (Sykes et al., 2016 [4]). The mechanism through which a reduction in de novo

pyrimidine biosynthesis modulates myeloid differentiation is not clear. The differentiation effect of DHODH inhibitors appears to involve a combination of inhibition of nucleic acid synthesis, cell-cycle arrest, and changes in the post-translational glycosylation of important protein targets.

Activated and proliferating T-cells have a particular dependence on nucleotide synthesis and nucleotide pools (Cohen et al., 1983 [15], Quéméneur et al., 2003 [16]), thus additional leukemias that may also benefit from brequinar's mechanism of action include T-cell lymphoblastic leukemia (T-ALL), bi-lineal leukemia (BLL), and mixed phenotypic acute leukemia (MPAL).

3.3 BREQUINAR

It is well known that brequinar is a potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate. Ultimately, the rationale to use brequinar for the treatment of multiple solid tumors did not translate into efficacy after extensive clinical development and the project was terminated by DuPont in 1994. Clear Creek Bio exclusively licensed the historic data from Bristol Myers Squibb (that acquired DuPont in 2001).

Sykes et al. (Sykes et al., 2016 [4]) showed that brequinar's pro-myeloid differentiation activity might be useful for the treatment of AML. Utilizing a high throughput screening technique, brequinar was identified as a compound that overcame arrest of myeloid differentiation. Brequinar triggers myeloid differentiation *in vitro* and *in vivo*. Brequinar was highly active *in vivo*, as demonstrated in syngeneic murine AML models (HoxA9+Meis1 and MLL/AF9) as well as xenotransplant AML models (THP1, HL60, MOLM13, OCI/AML3). In an aggressive MLL/AF9 murine model of AML, treatment with brequinar promoted myeloid differentiation, reduced leukemic cell burden, and improved overall survival. Brequinar also led to a reduction in the number of leukemia stem cells, reduced colony-formation level, and depleted the number of leukemia-initiating cell level.

In addition, Sykes and colleagues demonstrated that treatment with brequinar was better-tolerated and more effective than treatment with cytotoxic chemotherapy in animal models. Brequinar was given for many weeks without cumulative toxicity. The effect of brequinar and DHODH inhibition on normal cells was also assessed through study of competitive bone marrow transplantation assays. Mice were treated with brequinar, 5-fluorouracil (5-FU), or induction chemotherapy, and their bone marrow was transplanted in competition (1:1) with normal (untreated) bone marrow to gauge the effect of therapy on hematopoietic stem cell (HSC) function. The fitness of HSCs from mice treated with brequinar were functionally equivalent to those of untreated mice when compared to that of HSCs exposed to 5-FU and induction chemotherapy, which promoted a marked decrease in fitness.

Sykes et al. administered brequinar at a dose and schedule (every 72 hours) that was non-toxic to the animals yet led to eradication of the leukemia cells. This schedule of administration was based on data demonstrating that the pro-differentiation effect of brequinar required a period of sustained DHODH-inhibition of approximately three days. This observation suggests that brequinar's efficacy depends on producing approximately 72-hours "time-above-threshold" to maintain sustained DHODH inhibition. The hypothesis is that pyrimidine starvation via inhibition of DHODH for approximately 72 hours elicits pro-myeloid differentiation and leads to the anti-leukemia efficacy of brequinar.

Sykes et al. also showed that normal cells could tolerate longer periods of pyrimidine starvation than their leukemic counterparts. The proposed dosing regimen of brequinar in this clinical trial, CCB-01, is intended to take advantage of the different sensitivity of normal and leukemic cells and thus spare normal cells while eradicating leukemic cells.

A pharmacodynamic marker of enzyme inhibition (i.e. target engagement) is required to accomplish this type of rational dosing approach. Sykes and colleagues demonstrated how DHODH inhibition could be monitored by the accumulation of the substrate DHO. Indeed, inhibition of the DHODH enzyme led to the rapid accumulation of intracellular DHO, which was reflected by accumulation of DHO in plasma hence the rationale for measuring plasma DHO as the pharmacodynamic marker in CCB-01.

Given this new information, real-time monitoring of target engagement via plasma DHO of DHODH inhibition in each patient should permit identification of a brequinar dose that is both efficacious and well-tolerated. Maintaining intermittent DHODH inhibition for prolonged treatment cycles may be efficacious compared to previous studies using short periods and high doses followed by long periods of recovery.

The prior data on the clinical evaluation of brequinar in patients with multiple solid tumors provides valuable safety data that supports the safety of the proposed dosage regimen. Brequinar has not been studied clinically in myeloid malignancies in the past. Given encouraging pre-clinical results, brequinar has been evaluated in phase 1 and phase 2 trials of more than 800 patients with advanced solid tumor malignancies (Arteaga 1989 [5], Burris 1998 [6], Noe 1990 [7], Schwartsmann 1990 [8]). These studies indicated a lack of efficacy for brequinar at the doses and schedules evaluated. However, many of these trials studied brequinar administered as a single, high dose infusion given weekly or daily x 5 days every 3-4 weeks or every day for 21 days. The lack of efficacy in the previous trials may have been due to the narrow therapeutic window with the high doses studied, and to the inability, or lack of knowledge, to use a pharmacodynamic marker such as plasma DHO to fine-tune a therapeutic window based on differential pyrimidine starvation of myeloid precursors versus normal cells.

3.4 RIBAVIRIN

Ribavirin is known to inhibit inosine-5'-monophosphate dehydrogenase (IMPDH), the enzyme that catalyzes the conversion of inosine 5'-phosphate (IMP) to xanthosine 5'-phosphate (XMP),

the first committed and rate-limiting step in the de novo synthesis of guanine nucleotides. Ribavirin plays an important role in the regulation of cell growth and is itself important in purine metabolism (Kentsis et al., 2005 [20]; Assouline et al., 2009 [17]; Tan et al., 2008 [23]). Ribavirin is marketed in combination with interferon alfa-2b for the treatment of chronic hepatitis C (ribavirin generic SPC, Appendix H, Section 15.8). Ribavirin's ability to target the translation of oncogenes, particularly through inhibition of the eukaryotic translation initiation factor eIF4E, suggests that ribavirin may also be an effective cancer therapy (Kentsis et al., 2004 [21]; Kentsis et al., 2005 [20]; Assouline et al., 2009 [17]; Borden, 2008 [19]). Elevated levels of eIF4E are found in M4/M5 AML specimens (Assouline et al., 2009 [17]; Topisirovic et al., 2005 [22]; Topisirovic et al., 2003 [24]), suggesting that AML specimens have developed an oncogene dependency on eIF4E. In contrast, monocytes from healthy individuals do not have higher eIF4E and ribavirin did not affect their growth.

Ribavirin's possible anti-cancer effect was explored in a Phase II clinical trial, where Assouline et al. demonstrated that ribavirin treatment in poor prognosis AML patients led to substantial clinical benefit (2009 [17]). A total of 13 patients were treated at ribavirin daily starting doses of 1000 mg/day with escalation to 2800 mg/day. Several patients responded to ribavirin monotherapy with one complete remission, two partial remissions, two blast responses, and four stable diseases out of 11 evaluable patients. Although hemolytic anemia has been reported in connection with ribavirin treatment in hepatitis C patients, this reaction was not observed in the AML patients in this study. Additionally, no other ribavirin-related toxicities were observed for any patients in the trial, even after 9 months of treatment (Assouline et al., 2009 [17]).

Although Borden and colleagues reported a benefit for ribavirin monotherapy as presented above, these researchers suggested that it would be important to increase the response rate as well as the duration of clinical responses (2010 [19]). After the monotherapy trial, Assouline and colleagues therefore opened a trial of ribavirin and low dose cytarabine (LDAC) in relapsed and refractory AML (2015 [18]). A total of 29 subjects were treated with twice-daily doses of 1000, 1400, 1800 or 2200 mg ribavirin continuously and twice-daily 10 mg or 20 mg LDAC for ten days of every 28-day cycle. The combination was tolerated with no unexpected adverse events. As reported in this study, hemolytic anemia that resolved on discontinuation of ribavirin was observed in 4 (14%) of subjects at ribavirin doses of 1000 (n = 1), 1800 (n = 1), and 2200 mg (n = 2). Ribavirin with low dose cytarabine (LDAC) combination treatment in this study resulted in two complete remissions, one partial remission and two blast responses. Their recommended phase II dose was twice-daily 1400 mg ribavirin and twice-daily 10 mg LDAC.

The promising early results for ribavirin for treatment of AML in both monotherapy and combination settings led us to investigate the preclinical efficacy of a brequinar/ribavirin combination therapy (brequinar IB [9]), and this combination approach will be added to this protocol beginning with Cohort 3.

3.5 RATIONALE FOR THE PLANNED TRIAL

This study is designed to obtain safety and efficacy data for brequinar in patients with AML and other hematologic malignancies including T-ALL, BLL, and MPAL as these diseases may benefit from brequinar and/or from a combination of brequinar and ribavirin treatment.

Subject Population

The population for this study is patients 18 years of age or older, with relapsed/refractory AML by World Health Organization classification and other hematologic malignancies including T-ALL, BLL, and MPAL that have failed prior standard therapy and for which no standard therapies are available that result in a durable remission.

Study Treatments

This is an open label study of oral brequinar using intra-subject dose adjustment. The possible benefit of brequinar in AML and other hematologic cancers has been previously discussed (Sykes et al., 2016).

Ribavirin will be added in Cohort 3 as well as the expansion cohort, to be administered in combination with brequinar. As discussed above, ribavirin's efficacy in AML as well as its apparent lack of toxicity as a single agent in the AML population (Assouline, et al; 2009 [17]) and its lack of additive toxicity in a preclinical model (Brequinar IB [9]) make it an attractive combination therapy. Furthermore, while brequinar inhibits a key step (DHODH) in pyrimidine synthesis, ribavirin inhibits a key step (IMPDH) in purine synthesis as well as acts to inhibit cap-dependent translation. In this manner, both sides of nucleotide synthesis are targeted as well as those transcripts that rely on cap-dependent translation.

Dosing of brequinar and ribavirin as well as the dose-adjustment schemes are presented in detail in Section 8.5.

3.5.1 Brequinar Starting Dose Selection

The rationale underlying the proposed dosage regimen for brequinar and the use of plasma DHO to guide dosing is the prior demonstration using nonclinical models by Sykes et al. (2016) [4] that malignant cells are more sensitive than normal cells to periods of DHODH inhibition. The objective is to identify a dose and regimen of brequinar that maintains suppression of DHODH adequate to induce differentiation and stop myeloid proliferation but avoid harming normal cells. These features have been realized in vivo in animal models. Specifically, intermittent dosing that preserved elevated levels of the metabolite DHO markedly reduced AML cells, preserved normal hematopoietic stem cells, and improved animal survival. These recent findings and historic pharmacokinetic (PK) and safety data from humans support the planned approach.

Rather than intermittent high doses as were given by DuPont, Clear Creek will use relatively low doses and prolonged exposure to brequinar. There will not be a lengthy conventional rest period as is generally required between infrequent high doses. There will instead be twice-weekly administration of lower doses with a dosing interval that allows enough time for normal cells to recover from or avoid pyrimidine starvation in between the periods of DHODH inhibition. Based on its average half-life of 10.5 hours and what has been observed in the clinical PK data (see the Brequinar IB [9]), brequinar plasma levels return to baseline at about 3.5 days or 84 hours after an oral dose. For this reason, the proposed clinical study includes a twice-weekly schedule of brequinar dosed approximately every 84 hours, while measuring brequinar PK and plasma DHO to fine-tune the dose that ensures sustained DHODH inhibition while avoiding adverse effects to normal cells.

Safety data from previous oncology clinical studies of brequinar (see brequinar IB [9], Section 5) with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks suggested that a starting dose for Cohort 1 of 500 mg/m^2 p.o. would be safe and well-tolerated in subjects with AML. This 500 mg/m^2 starting dose was used in Cohorts 1 and 2 in this protocol, however Cohorts 1 and 2 results indicate that a starting dose of 350 mg/m^2 should allow subjects to more rapidly progress to the desired twice weekly dosing. The starting brequinar dose for the remainder of Cohort 2 was therefore reduced to 350 mg/m^2. The starting brequinar dose for Cohort 3 and the expansion cohort will also be 350 mg/m^2. This starting dose may be decreased, if necessary, to 200 mg/m^2 following the dose adjustment guidelines found in Section 8.5.1. After moving to twice weekly dosing, each subject's subsequent brequinar dose is to be adjusted depending on the safety, tolerability, and DHO level obtained during treatment. See Section 8.5.

3.5.2 Ribavirin Dosing

For Cohort 3 and the expansion cohort, ribavirin 1000 mg BID will be added in combination with brequinar following a brequinar only period of approximately 3 to 6 weeks. Assuming acceptable safety, the ribavirin dose is to be escalated by 400 mg/BID approximately every 4 weeks to a maximum of 1800 mg/BID. Ongoing Cohort 2 subjects who have reached twice weekly dosing with 84h DHO < 5000 ng/mL may begin the ribavirin combination immediately. See Section 8.

3.6 RISK/BENEFIT OF BREQUINAR

As presented in the brequinar IB [9], more than 800 patients have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. Study results have not shown evidence of efficacy in solid tumors at the doses and regimens studied. However, the preclinical work of Sykes et al (2016) [4] have demonstrated the efficacy of brequinar in a mouse model of leukemia, indicating that brequinar may be effective in patients with this type of leukemia. It is for this reason that study CCB-01 will study patients with AML.

A universal hallmark of leukemia is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Therapies that can overcome differentiation arrest caused by DHODH represent a powerful treatment strategy. A potential benefit of brequinar treatment is that brequinar has been identified as a compound that can inhibit DHODH.

The major risk associated with brequinar is myelosuppression, particularly a decrease in platelet count. Patients with hematologic malignancies typically have a low platelet count due to their disease, and there is a risk that treatment with brequinar may worsen existing thrombocytopenia.

3.7 RISK/BENEFIT OF RIBAVIRIN

As presented above, ribavirin was associated with several complete, partial, and blast responses in two clinical trials of AML patients (Assouline et al., 2009 [17]; Assouline et al., 2015 [18]).

Risks associated with ribavirin administration in 40% or greater of adult patients receiving ribavirin included fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. Hemolytic anemia occurred in approximately 13% of adult patients receiving ribavirin with interferon for hepatitis C; this effect was not observed in the 13 AML patients treated with ribavirin (Assouline et al., 2009) with ribavirin monotherapy, but was reported in 14% of patients (4 of 29) in the Assouline et al., 2015 [18] study of ribavirin and low dose cytarabine. Additional safety information is provided in the ribavirin generic SPC (Appendix H Section 15.8).

3.8 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

In studies utilizing the weekly schedule of administration of brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing. Symptoms of tumor lysis syndrome have not previously been reported following exposure to brequinar, however clinicians will monitor for and treat this condition should it arise per the guidelines presented in Section 10.9. An increased risk of infection may occur due to the myelosuppressive effects of brequinar (particularly neutropenia); infection prophylaxis and treatment are described in Sections 10.10 and 10.11. Differentiation syndrome has been seen in other pro-differentiating agents and will be closely followed as described in Section 10.7.

Risks associated with ribavirin administration in hepatitis C patients who also received interferon are presented in the ribavirin generic SPC found in Appendix H, Section 15.8.

3.9 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. No formal interaction studies have been conducted for these

medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

There is limited experience with ribavirin for treatment of AML and other hematologic malignancies and no formal interaction studies have been conducted for use of ribavirin with concomitant medications that are typical in cancer patients. However, experience with use of ribavirin and interferon in treatment of hepatitis C has concluded that ribavirin should not be given with nucleoside reverse transcriptase inhibitors such as didanosine or with azathioprine. Ribavirin should be taken with food. See ribavirin generic package insert, Appendix H Section 15.8.

3.9.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar Investigator's Brochure [9]; nonclinical data on file with Clear Creek).

Results of in vitro studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based interactions (ribavirin generic SPC Appendix H Section 15.8).

3.10 STEPS TO BE TAKEN TO CONTROL OR MITIGATE RISKS

Guidelines for the prevention, monitoring and treatment of differentiation syndrome, tumor lysis syndrome, infection prophylaxis and growth factor support are provided in Section 10. Haptoglobin levels will be utilized to monitor possible hemolysis which was reported in some subjects taking ribavirin for hepatitis C (Vlierberghe et al., 2001 [26]) and some AML patients (Assouline et al., 2015 [18]). All subjects will be treated by highly experienced hematologic oncologists familiar with the treatment of pancytopenia and hemolytic anemia and their side effects.

4 TRIAL OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine the safety and tolerability of brequinar alone and in combination with ribavirin and the dihydroorotate dehydrogenase (DHODH) inhibitory activity of brequinar in adult patients with AML and other hematologic malignancies.

4.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- 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 Döhner et al., 2017 [10] and the Report of the National Cancer Institute-sponsored Workshop, Cheson et al., 1990 [25]) 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
- To characterize the pharmacokinetic (PK) profile of brequinar.
- To characterize the DHO plasma levels after oral dosing with brequinar.

4.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

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

5 TRIAL DESIGN

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 alone and in combination with ribavirin in adult subjects with AML and other hematologic malignancies. The study will also assess the inhibition of DHODH and the PK profile of brequinar in plasma. Intra-subject dosing may be adjusted based on safety/tolerability, brequinar pharmacokinetics (PK), and DHO levels.

Up to 27 subjects are planned to be entered in this trial. Cohort 1 enrolled 5 subjects. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly. Three Cohort 2 subjects discontinued from the study prior to Day 43 and may be replaced.

Although the 500 mg/m^2 starting dose of brequinar was well tolerated by many subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses lower than 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, any newly enrolled Cohort 2 subjects are to start with 350 mg/m^2 once weekly. Approximately 3 additional subjects may be enrolled into Cohort 2. If Cohort 3 regulatory approval is achieved prior to completing Cohort 2, it is not required to complete Cohort 2 before beginning enrollment into Cohort 3. Cohort 2 subjects who are active in the study at the time of regulatory approval may roll over into Cohort 3.

Cohort 3 will enroll approximately 6 to 9 subjects and may be followed by an expansion cohort of approximately 6 to 12 subjects. Cohort 3 and the Expansion Cohort will use the 350 mg/m^2 starting dose.

After both the brequinar 48h PK and 72h DHO level meet criteria described in the Individual Dose Adjustment Guidelines below, the subject is to move to twice weekly brequinar dosing on a continuing basis as tolerated. After moving to twice weekly brequinar dosing, the brequinar dose is to be reduced if needed per the algorithm below to achieve an 84h DHO of < 5000 ng/mL. After achieving a brequinar twice weekly dose that achieves 84h DHO < 5000 ng/mL, ribavirin dosing will begin at 1000 mg BID in combination with twice weekly brequinar. After initiating ribavirin dosing, the brequinar dose will continue to be adjusted using the dosing adjustment algorithm below. After brequinar has reached a stable dose, ribavirin will be increased 400 mg BID every 4 weeks to a maximum of 1800 mg BID.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters. Haptoglobin levels may be utilized to assess hemolytic anemia.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression. Subjects who discontinue for any reason prior to at least 4 weeks of the brequinar/ribavirin combination may be replaced. Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow

sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters.

Study procedures are presented in detail in Section 8.

6 TRIAL ENDPOINTS

6.1 PRIMARY ENDPOINT

- Safety/tolerability and DHO level relationship with safety and therapeutic brequinar levels

6.2 SECONDARY ENDPOINTS

- Rates of treatment-emergent adverse events.
- Overall Response Rate (ORR) including CR, CRh, CRi, MLFS, or PR
- Event-free survival (EFS).
- Duration of response
- PK profile of brequinar.
- DHO plasma profile.

6.3 EXPLORATORY ENDPOINTS

- 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

7 TRIAL POPULATION

7.1 NUMBER OF SUBJECTS

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 27 subjects have completed the study.

7.2 INCLUSION CRITERIA

1. Willing and able to provide written informed consent for the trial.

2. Patients 18 years of age or older, with relapsed/refractory AML by World Health Organization (WHO) classification, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL) and who have exhausted available therapy.

3. ECOG Performance Status 0 to 2.

4. 12-lead ECG with no clinically unacceptable findings; adequate cardiac function/NYHA Class 0 to 2.

5. Adequate hepatic function (unless deemed to be related to underlying leukemia).

    a. Direct bilirubin $\leq$ 2 x ULN

    b. ALT $\leq$ 3 x ULN

    c. AST $\leq$ 3 x ULN

6. Adequate renal function as documented by creatinine clearance $\geq$ 50 mL/min based on the Cockcroft-Gault equation.

7. In the absence of rapidly proliferative disease, the interval from prior leukemia-directed therapy to time of first dose of study drug will be at least 7 days for cytotoxic or non-cytotoxic (immunotherapy) agents. Use of supportive care measures per institution's standard of care is permitted at any time.

8. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of brequinar administration.

9. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

7.3 EXCLUSION CRITERIA

1. Patients in need of immediate leukapheresis.

2. Any concurrent uncontrolled clinically significant medical condition, laboratory abnormality, or psychiatric illness that could place the participant at unacceptable risk of study treatment.

3. QTc interval using Fridericia's formula (QTcF) ≥ 470 msec. Participants with a bundle branch block and prolonged QTc interval may be eligible after discussion with the medical monitor.

4. Pre-existing liver disease.

5. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

    a. Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia.

6. Presence of graft versus host disease (GVHD) which requires an equivalent dose of ≥ 0.5mg/kg/day of prednisone or therapy beyond systemic corticosteroids (e.g. cyclosporine or other calcineurin inhibitors or other immunosuppressive agents used for GVHD).

7. Active cerebrospinal involvement of AML, T-cell leukemia (T-ALL), bi-lineal leukemia (BLL), or mixed phenotypic acute leukemia (MPAL).

8. Diagnosis of acute promyelocytic leukemia (APL).

9. Clinically active hepatitis B (HBV) or hepatitis C (HCV) infection.

10. Severe gastrointestinal or metabolic condition that could interfere with the absorption of oral study medication.

11. Prior malignancy, unless it has not been active or has remained stable for at least 2 years. Participants with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed. Participants with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if at the active surveillance stage, if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.

12. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.

13. Documented hemoglobinopathy.

7.4 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

Up to 27 subjects are planned to be entered in this trial. Cohort 1 enrolled 5 subjects with a starting dose of 500 mg/m^2 twice weekly. Cohort 2 enrolled 6 subjects with a starting dose of 500 mg/m^2 once weekly. Three Cohort 2 subjects discontinued from the study prior to Day 43 and may be replaced.

Although the 500 mg/m^2 starting dose of brequinar was well tolerated by most subjects, several subjects took as many as 4 to 5 weeks to achieve twice weekly dosing at doses lower than 500 mg/m^2. In order to more quickly achieve the desired twice weekly dosing schedule, any newly enrolled Cohort 2 subjects are to start with 350 mg/m^2 once weekly. Approximately 3 additional subjects may be enrolled into Cohort 2. If Cohort 3 regulatory approval is achieved prior to completing Cohort 2, it is not required to complete Cohort 2 before beginning enrollment into Cohort 3. Cohort 2 subjects who are active in the study at the time of regulatory approval may roll over into Cohort 3.

Cohort 3 will enroll approximately 6 to 9 subjects and may be followed by an expansion cohort of approximately 6 to 12 subjects. Cohort 3 and the Expansion Cohort will use the 350 mg/m^2 starting dose.

After both the brequinar 48h PK and 72h DHO level meet criteria described in the Individual Dose Adjustment Guidelines below, the subject is to move to twice weekly brequinar dosing on a continuing basis as tolerated. After moving to twice weekly brequinar dosing, the brequinar dose is to be reduced if needed per the algorithm below to achieve an 84h DHO of < 5000 ng/mL. After achieving a brequinar twice weekly dose that achieves 84h DHO < 5000 ng/mL, ribavirin dosing will begin at 1000 mg BID in combination with twice weekly brequinar. After initiating ribavirin dosing, the brequinar dose will continue to be adjusted using the dosing adjustment algorithm below. After brequinar has reached a stable dose, ribavirin will be increased 400 mg BID every 4 weeks to a maximum of 1800 mg BID.

Safety will be assessed utilizing physical examination, vital sign measurements, safety laboratory testing, 12-lead ECGs and bone marrow sampling. Bone marrow sampling will also be utilized to measure response. Tolerability will be assessed by spontaneously reported and elicited adverse events. DHO level will be measured using a validated assay. Brequinar PK will be analyzed using standard PK parameters. Haptoglobin levels may be tested to assess hemolytic anemia.

Dosing will continue for up to 12 months in the absence of unacceptable toxicity or disease progression. Subjects who discontinue for any reason prior to at least 4 weeks of the brequinar/ribavirin combination may be replaced.

8.1 DESCRIPTION OF STUDY MEDICATIONS

8.1.1 Brequinar

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be determined on a mg/m^2 basis and will be adjusted based on tolerability, safety, brequinar PK, and DHO levels. Brequinar capsules should be taken whole; they should not be crushed or chewed. If the participant forgets to take the daily dose, he/she should make up the dose within 24 hours. Any medication remaining from extra supplies or missed doses should not be taken beyond the last scheduled day of brequinar administration but should be documented in the subject diary and returned by the participant for drug accountability purposes.

8.1.2 Ribavirin

Ribavirin will be supplied as 200 mg capsules. Dosing is a flat dose beginning at 1000 mg BID, escalating to 1400 mg and 1800 mg BID approximately every 4 weeks after a stable dose of brequinar has been achieved. Ribavirin should be taken with food (ribavirin generic SPC, Appendix H, Section 15.8).

8.2 TREATMENT ADMINISTRATION

Five subjects were enrolled in the now-completed Cohort 1. All subjects were dosed with twice weekly brequinar 500 mg/m^2 for a range of 2 to 16 doses (one to 8 weeks). No additional subjects will be enrolled into Cohort 1. A total of 6 subjects were treated in Cohort 2 with a starting dose of 500 mg/m^2 once weekly. These 6 Cohort 2 subjects took brequinar once weekly for at least two weeks (two total doses). Brequinar exposure and DHO levels were used to adjust the brequinar dose (if necessary) to meet brequinar PK and 72h DHO criteria described in Section 8.5.1. Subjects then moved to twice-weekly dosing (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis. The brequinar dose was further adjusted if needed using the 84h DHO (trough) Criteria shown in Section 8.5.4.

Three Cohort 2 subjects were not evaluable due to early discontinuation. Approximately 3 additional subjects with a starting dose of 350 mg/m^2 may be enrolled into Cohort 2 to replace these subjects. It is not necessary to complete enrollment in Cohort 2 if Cohort 3 regulatory approval is available before completing Cohort 2.

For Cohort 3 and the expansion cohort, ribavirin will be added in combination with brequinar following a brequinar only period of approximately 3 to 6 weeks. Ribavirin dosing will begin as soon as brequinar dosing has moved to twice weekly and the twice weekly 84h DHO (DHO 84 hours after a twice weekly brequinar dose) is confirmed to be < 5000 ng/mL. Cohort 3 may be followed by an expansion cohort of approximately 6 to 12 subjects. Brequinar PK and DHO samples will be obtained during Week 1. The results from Week 1 will be used to make decisions about the Week 2 dose and schedule. Subjects who meet the twice weekly brequinar PK and 72h

DHO criteria in Week 1 may proceed to twice weekly dosing with 350 mg/m^2 in Week 2. For subjects whose brequinar PK and DHO levels do not meet the twice weekly criteria or who have unacceptable safety, decrease the dose to 200 mg/m^2 once weekly. For these subjects, brequinar PK and DHO samples will also be obtained once daily on Days 1 – 4 during Week 2 (or when dosing resumes following an AE), and the Week 2 results will be used to make decisions about Week 3. If a subject still does not meet the twice weekly criteria when dosed at 200 mg/m^2 once weekly, discontinue the subject. Subjects who discontinue for any reason prior to at least 4 weeks of the combination may be replaced with sponsor permission. The twice weekly brequinar dose may be adjusted as needed to establish the 84h DHO in the target range.

Cohort 2 subjects who are ongoing at the time of Cohort 3 IRB approval (CCB-01 Amendment No. 08) and have begun twice weekly brequinar dosing may roll over into Cohort 3 and immediately begin ribavirin in combination with brequinar.

Each dose of study drug is to be taken with approximately 240 mL of water. The ribavirin study medication should be taken with food. Each dose will generally consist of multiple capsules; the study medication does not need to be swallowed all at once but can be spread over up to approximately 15 minutes as needed. The chosen dosing schedule needs to accommodate clinic visits as well as shipping and receipt of the brequinar/DHO samples and results needed for dosing adjustments. Sample processing and shipping procedures will be addressed in a separate laboratory manual.

8.3 SAFETY/TOLERABILITY

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Cohort 1 had a fixed starting dose of 500 mg/m^2 with no dose escalation permitted. Cohort 2 started with 500 mg/m^2 once weekly and had adjustments made to dose and dose frequency using safety/tolerability, brequinar exposure (PK), and DHO levels. As described above, any replacement Cohort 2 subjects will start at 350 mg/m^2 once weekly with the goal of moving rapidly to twice weekly dosing. Cohort 3 and Expansion Cohort brequinar subjects will have a starting dose of 350 mg/m^2. Ribavirin dosing will begin at 1000 mg BID. See Section 8.5 for brequinar dose adjustments and ribavirin dosing instructions.

Safety at the subject level is defined in Section 8.3.1; hematologic toxicity is defined in Section 8.3.2. The following adverse events are commonly observed in patients with hematologic malignancies and should be differentiated from possible adverse effects of brequinar: fatigue, fever, thrombocytopenia and other cytopenias, infection, pallor, shortness of breath, weight loss, night sweats, and anorexia. Any of these events can be serious in nature and may result in death. Disease progression is considered a lack of efficacy rather than an adverse event. Death from disease progression is to be reported as presented in Section 10. Hemolysis was reported in approximately 13% of subjects taking ribavirin with interferon for hepatitis C (see Appendix H, Section 15.8). A decrease in haptoglobin to below the lower limit of quantification for the local laboratory will be used to alert clinicians to the possibility of hemolysis associated with ribavirin

treatment, which may lead to discontinuation of ribavirin dosing after discussion with the Sponsor and Medical Monitor.

Adverse events commonly observed in patients treated with brequinar are provided in the Investigator's Brochure and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 subjects treated once-weekly (DuP 785-012), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In most instances, drug related toxicities were clinically manageable and reversible upon discontinuation of brequinar treatment. In a study where brequinar was dosed twice-weekly to solid tumor subjects, no drug-related deaths occurred. Stomatitis/mucositis was observed in 13 of the 19 (68%) patients across all doses. Mild to moderate (Grades 1 and 2) stomatitis was observed in 10 patients with a more severe (Grade 3) stomatitis seen in 3 patients at doses over 600 mg/m^2. One patient at 600 mg/m^2 had drug discontinuation due to drug-related stomatitis. Myelosuppression was the main dose-limiting toxicity (DLT) with thrombocytopenia (Grades 1-4), observed after 2 to 9 doses above 600 mg/m^2. Any of these events reported with brequinar use can be serious in nature and may result in death.

Prescriptions can be provided in advance for supportive care for common brequinar-related AEs such as mucositis.

Adverse Events associated with ribavirin administration in 40% or greater of adult patients receiving ribavirin and interferon in the hepatitis C studies included fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. Hemolytic anemia occurred in approximately 13% of adult hepatitis C patients receiving ribavirin with interferon. Hemolytic anemia was observed in 0 of 13 AML patients treated with ribavirin monotherapy (Assouline et al., 2009 [17]) and 4 of 29 (14%) of patients treated with ribavirin and LDAC (Assouline et al., 2015 [18]). Additional safety information is provided in the ribavirin generic SPC (Appendix H Section 15.8).

8.3.1 Safety/Tolerability – Subject Level

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Acceptable safety/tolerability for a subject through Day 42 is defined as no ≥ Grade 3, treatment-emergent, study-drug-related, non-hematologic adverse events. Due to the expected hematologic profile associated with AML and other hematologic malignancies, hematologic AEs of any grade will not be considered a DLT during the first 42 days of dosing (i.e., assessed at the visit conducted on Day 43). Exceptions to the non-hematologic Grade 3 criterion are provided in Table 8-1.

If a dose is held due to safety/tolerability issues, the subject should continue to have scheduled visits and assessments.

If AEs have not resolved to ≤ Grade 2 after two weeks without dosing, dosing is to be discontinued for this subject.

Table 8-1. Exceptions to Grade 3 Nonhematologic AEs

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 completion of the first 42 days of treatment, the definition of unacceptable safety is expanded to include signs of hepatotoxicity (≥ Grade 2 toxicity for ALT and AST). Dosing is to be held for at least one week (i.e., two doses if twice weekly) for subjects who experience hepatotoxicity; dosing may resume only if the hepatotoxicity AE resolves to ≤ Grade 1 within two weeks. If the subject experiences a second episode of ≥ Grade 2 hepatotoxicity after resuming dosing, dosing is to be discontinued for that subject.

8.3.2 Hematologic Toxicity

After the subject has completed the first 42 days of treatment, the definition of unacceptable safety expands to include hematologic AEs defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. Febrile neutropenia is also excluded from the DLT definition for this population. For clinic visits when bone marrow sampling is scheduled, the timing of the bone marrow sampling can be adjusted to ensure that the results are available at the time of the clinic visit. Hemolytic anemia has been reported in approximately 13% of subjects taking ribavirin and interferon alfa-2a for hepatitis C. A decrease in haptoglobin level below the lower limit of normal (LLN) for the local laboratory will be used to trigger the investigation of possible hemolysis in subjects taking the brequinar/ribavirin combination or ribavirin alone and may lead to discontinuation of ribavirin after discussion with the Investigator, Sponsor and Medical Monitor. Haptoglobin testing should be conducted prior to administering any blood products transfusions when possible as transfusions may influence haptoglobin levels.

8.4 COHORT STARTING DOSES

Cohort 1 treated 5 subjects at 500 mg/m^2 twice weekly. Cohort 2 treated 6 subjects with this starting dose once weekly. Three Cohort 2 subjects discontinued prior to Day 43 and may be replaced using a starting dose of 350 mg/m^2. Cohort 3 and Expansion cohort subjects will have a starting dose of 350 mg/m^2. Each subject's brequinar dosing frequency and dose may be adjusted as shown in the following sections.

8.5 INDIVIDUAL DOSE ADJUSTMENT GUIDELINES

Pre-clinical evidence (Sykes et al., 2016 [4]) suggests that a twice-weekly dose is most likely to lead to efficacy, therefore the goal is to adjust the brequinar dose to allow all subjects to dose on a twice-weekly basis. In order to move to twice-weekly dosing as quickly as possible, Cohort 3 subjects will start with a once weekly dose of brequinar of 350 mg/m^2. If the subject meets twice weekly dosing criteria with this dose, move the subject move to twice weekly dosing with 350 mg/m^2 in Week 2. If the twice weekly criteria are not met in Week 1 or there is unacceptable safety, decrease the dose for Week 2 to 200 mg/m^2 (or when dosing resumes following an AE) and dose once. If the subject now meets dosing criteria with 200 mg/m^2, begin twice weekly dosing with 200 mg/m^2 in week 3 or as soon as safety is acceptable. If the twice weekly dosing criteria are not met with 200 mg/m^2, discontinue this subject. Subjects who meet twice weekly dosing criteria will dose twice weekly (approximately every 3.5 days, e.g., Monday morning and Thursday evening) on a continuing basis.

After beginning twice weekly dosing, the brequinar dose is to be further reduced (if needed) to achieve an 84h DHO < 5000 ng/mL.

Ribavirin dosing will begin when brequinar twice weekly dosing results in an 84h DHO < 5000 ng/mL. See "Ribavirin Dosing" below for further instructions regarding ribavirin dosing.

After starting ribavirin dosing, the twice weekly brequinar dose is to be further adjusted using the 84h DHO algorithm shown below. There is no upper or lower brequinar dose limit after achieving twice weekly dosing and ribavirin dosing has started. The 84h DHO level obtained 84 hours after a twice weekly brequinar dose will be used to adjust the next dose as needed. This brequinar dose adjustment may be made every two weeks, if necessary.

Dose increases and continued dosing must first meet acceptable safety requirements as described in Section 8.3.1. If unacceptable safety occurs, hold dosing until AE resolves to ≤ grade 2, reduce dose by 150 mg/m^2 and resume dosing. Discontinue the subject if a dose reduction leads to a dose of zero or the available capsule strengths cannot accommodate the designed mg/m^2 dose. If brequinar PK or DHO levels are not available for dose adjustment decisions, hold dosing until results are available.

The dose adjustment procedures and criteria may be revised after each preceding cohort's safety, brequinar PK, DHO plasma levels, and bone marrow results have been reviewed. The dose adjustment process and criteria are described in the following sections.

8.5.1 Brequinar Exposure (BRQ PK) and 72h DHO Criteria to Set Twice-Weekly Dosing

Both brequinar exposure (pharmacokinetics, PK) and dihydroorotate (DHO) levels are utilized to set the twice weekly dose. For Cohort 3, the initial goal is to identify a dose that results in brequinar PK approximately 48 hours after dosing of less than or equal to 5 mcg/mL (48h BRQ PK ≤ 5 mcg/mL). Next check the DHO results obtained 48 and 72 hours after dosing. The twice weekly DHO criteria are that the DHO obtained 72 hours after dosing must be less than the DHO obtained 48 hours after dosing (i.e., on a downward slope). In addition, the DHO level at 72 hours must be less than 5000 ng/mL. To summarize, 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL. See the algorithm to set the twice weekly dose for Cohort 3 in Table 8-2 and Figure 8-1.

Table 8-2. Algorithm to Set Twice-Weekly Dose for Cohort 3/Expansion Subjects (Starting Dose 350 mg/m^2)

Brequinar PK*	72h DHO**	Action
48h BRQ PK > 5 mcg/mL	NA	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess BRQ PK
BRQ PK Criteria Met*	72h DHO Criteria NOT MET**	Decrease dose to 200 mg/m^2 and continue weekly dosing, reassess 72h DHO criteria
BRQ PK Criteria Met*	72h DHO Criteria MET**	Begin twice-weekly dosing Week 2 or after

* Brequinar PK (BRQ PK) Criteria for Cohort replacements and Expansion Cohort: 48h BRQ ≤ 5 mcg/mL

**72h DHO Criteria: 72h DHO < 48h DHO (on a downward slope) AND 72h DHO <5000 ng/mL

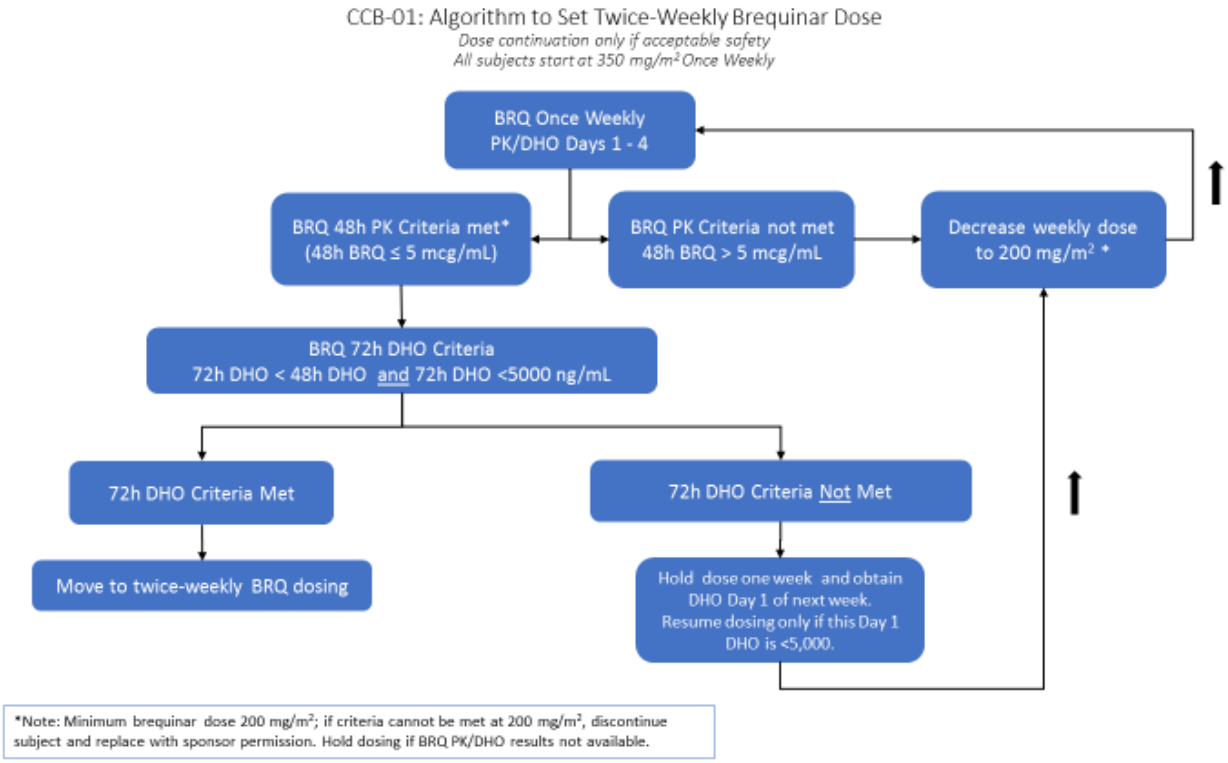

Figure 8-1. Algorithm to Set Twice-Weekly Dose

8.5.2 Ribavarin in Combination with Brequinar

Beginning with Cohort 3 and the expansion cohort, ribavirin will be added beginning at 1000 mg BID following the initial brequinar only period. Ribavirin dosing will begin as soon as brequinar dosing has moved to twice weekly and the twice weekly 84h DHO (DHO 84 hours after a twice weekly brequinar dose) is confirmed to be < 5000 ng/mL, expected to be a period of approximately 3 to 6 weeks. See Figure 8-2.

8.5.3 Ribavirin Dose Adjustment

Ribavirin dosing in combination with brequinar will be continued at 1000 mg BID for approximately 4 weeks or until brequinar has reached a stable twice weekly dose, whichever is longer. Approximately 4 weeks after reaching the twice weekly stable brequinar dose, increase the ribavirin dose 400 mg BID. Increase the ribavirin dose another 400 mg BID after another 4 weeks to a total of 1800 mg BID. This dose will continue until the subject meets the criteria for study discontinuation (see Section 8.9). If suspected ribavirin-related toxicity occurs, hold ribavirin dosing for 2 weeks. If the ribavirin-related toxicity resolves to < Grade 2, decrease the ribavirin dose by 400 mg BID and resume dosing at the reduced dose. See Figure 8-2. Either brequinar or ribavirin may continue to be administered as a single agent if either study drug is discontinued due

to unacceptable safety related to either agent. Cohort 2 subjects rolling over into Cohort 3 must meet the requirements for twice weekly dosing before beginning ribavirin dosing.

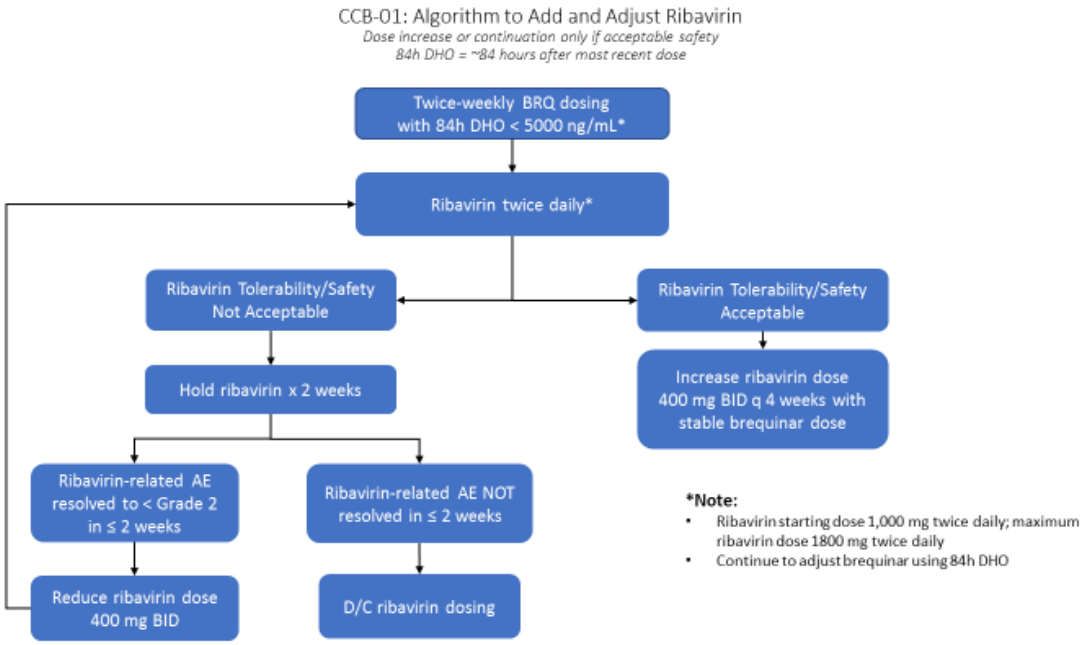

Figure 8-2. Algorithm to Add and Adjust Ribavirin

8.5.4 Dose Adjustment Using 84h DHO

After starting ribavirin dosing, the twice weekly brequinar dose is to be further adjusted using the 84h DHO twice weekly adjustment algorithm shown below. There is no upper or lower brequinar dose limit after achieving twice weekly dosing and ribavirin dosing has started. The 84h DHO level obtained 84 hours after a brequinar dose will be used to adjust the next dose as needed. This brequinar dose adjustment may be made every two weeks, if necessary.

This brequinar dose adjustment may be made on a continuing basis. If DHO levels are not available for dose adjustment decisions, confirm safety is acceptable but hold the dose until results are available. As soon as results are available, adjust dose as needed following criteria and resume dosing. Further adjustments are permitted using the 84h DHO results during twice weekly dosing. There is no maximum or minimum allowable dose during twice weekly dosing. See Table 8-3 and Figure 8-3.

Table 8-3. Algorithm to Adjust Twice-Weekly Dose using 84h DHO for Cohort 3 and Expansion Cohort

84h DHO Criteria	Action
84h DHO < 1500 ng/mL	Increase next week's dose by 75 mg/m^2
84h DHO ≥ 1500 ng/mL and < 5000 ng/mL	Stable Dose. Check 84h DHO weekly x 12 weeks then every 2 weeks. Adjust dose PRN per 84h DHO criteria.
84h DHO ≥ 5000 ng/mL	HOLD. Notify subject not to take next dose. Hold dosing for one week. If next Day 1 84h DHO is < 5000 ng/mL, decrease next dose by 75 mg/m^2 and resume twice-weekly dosing. If next Day 1 84h DHO ≥ 5000 ng/mL, no further dosing, discontinue the subject.

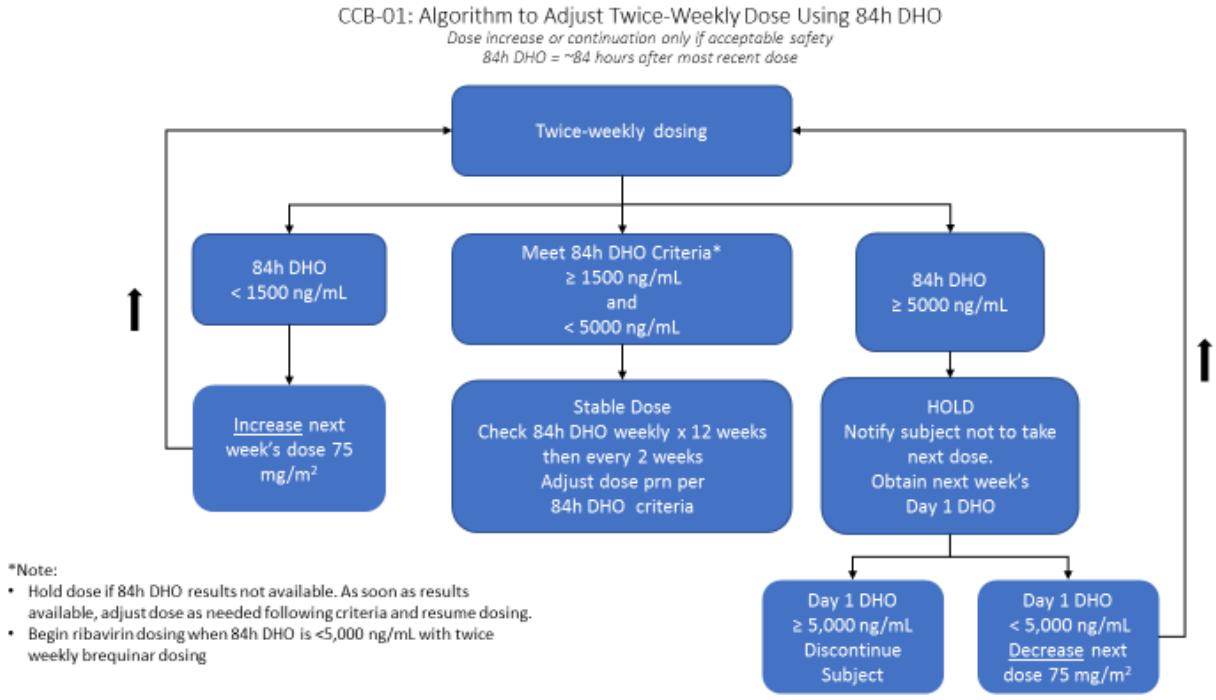

Figure 8-3. Algorithm to Adjust Dose Using 84h DHO

Each subject will continue twice-weekly dosing at the individually adjusted dose for up to 12 months (total time from first dose) in the absence of unacceptable toxicity or disease progression. Additional intra-subject brequinar dose adjustment is permitted at any time throughout the study based on safety/tolerability and 84h DHO levels. Subjects who discontinue for any reason prior to completing at least 4 weeks of combination therapy may be replaced.

8.6 MEDICATION/AE DIARY

The participant will be provided with a study calendar of events and will be required to maintain a medication diary of each dose of medication. Subjects will be instructed to record the date and time each dose of brequinar is taken, indicating if any doses are missed. Subjects will be instructed to record adverse events and changes in concomitant medications in the subject calendars/diaries.

Subjects will be instructed and reminded to bring the medication diary to each clinic visit for review. The diary will be returned to clinic staff at the end of each cycle and a new diary dispensed.

8.7 BONE MARROW BIOPSY

The participant will have a bone marrow sampling (aspiration and core biopsy) at baseline (prior to dosing), one for research purposes at the Week 4 visit (Day 22 ± 7 days), and one 4 weeks after initiating the combination with ribavirin (expected to be approximately Day 43 ± 7 days); thereafter, bone marrow sampling will be obtained every 12 weeks ± 7 days (or per institutional standard of care) and at the Final Visit. If a participant develops frank evidence of progression of disease during the course of treatment based on laboratory or clinical assessment, he/she will be discontinued from study treatment and can proceed with additional management off-study per discretion of the treating oncologist. If the results of the bone marrow sampling reveal disease progression at approximately Visit 7 (Day 43) (defined as 43 days after initiating treatment or after 6 complete weeks after initiating study drug treatment regardless of number of doses, but with at least 4 weeks of brequinar/ribavirin combination therapy), then the participant will be taken off treatment. Timing of the bone marrow biopsy procedure may be adjusted to ensure that results are available for any visit. Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Molecular analysis will be performed on the screening bone marrow samples.

8.8 EXPANSION COHORT

Following completion of Cohort 3, an expansion cohort of up to 6 to 12 subjects may be added to further define the dosing, BRQ PK and DHO criteria and assess the safety, tolerability, and biological activity of the dosing scheme.

The expansion cohort will follow the same visit procedures as Cohort 3.

8.9 STUDY DRUG DISCONTINUATION

If there is evidence of stable disease, partial response, or complete remission (CR, CRi, or CRh) at or prior to approximately Visit 7 (43 days, or at least 4 weeks after initiation of ribavirin) or with the agreement of the principle investigator and sponsor, the participant may continue with brequinar treatment until there is evidence of disease progression, intolerable toxicity, or for a maximum of one year. Study drug will be discontinued for an individual subject if there is evidence of unacceptable safety/tolerability that does not resolve to ≤ Grade 2 within 2 weeks after stopping brequinar or ribavirin dosing.

After treatment discontinuation, participants will be monitored for a minimum of 14 days after the last dose of brequinar or ribavirin or until they receive another treatment for their AML or other hematologic malignancy. Participants may discontinue treatment to receive a stem cell transplantation upon remission, if indicated.

Suspected drug-related toxicities that lead to discontinuation should be considered separately for brequinar and ribavirin. It is not required to discontinue the subject from the study if either brequinar or ribavirin must be stopped; the subject may continue on single agent therapy with agreement of the PI, Sponsor, and Medical Monitor.

The reason for study drug discontinuation will be recorded in the source document and the eCRF.

8.10 BREQUINAR PHARMACOKINETICS (PK)/DIHYDROOROTATE (DHO) PLASMA LEVELS/FLOW CYTOMETRY

Plasma samples for brequinar/DHO levels and peripheral blood for flow cytometry are to be obtained using the following schedule and as shown in Section 15.3:

- Cycle 1 Week 1: Day 1 (prior to dosing, and 1, 2, 4, and 6 hours after dosing), Days 2, 3, and 4 (approximately 24h, 48h, and 72h after dosing)
- Cycle 1 Week 2 (if needed due to dose reduction): Day 1 prior to dosing, Days 2, 3, and 4 (approximately 24h, 48h, and 72h after dosing).
- After starting twice-weekly dosing, obtain sample prior to dosing on Days 1 and 8 of each Maintenance Dose Cycle up to Week 12 from initial dose, then once every 2 weeks (i.e., Day 1 of each two-week Maintenance Dose Cycle).
- Final Visit: obtain brequinar, DHO, and flow cytometry samples.

The samples will be processed and shipped per the instructions in the laboratory manual. If the samples are drawn on a weekend, holiday, or after hours, obtain the samples on the specified study day and ship the samples as soon as possible. Directions regarding sample processing and shipping are presented in a separate laboratory manual.

8.11 CONCOMITANT MEDICATION/TREATMENT

Record the name, start date, indication for use, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. The use of other chemotherapeutic agents or anti-leukemic agents is not permitted during study with the following exceptions:

- Intrathecal chemotherapy for prophylactic use or maintenance of controlled CNS leukemia;

- Use of supportive care measures per institution's standard of care are permitted at any time including hydroxyurea for the purpose of leukemic cytoreduction.

Transfusions are to be recorded beginning from up to 2 weeks prior to first dose of study drug and ongoing throughout the individual's participation.

8.11.1 Gastric pH

Whenever possible, participants should discontinue proton pump inhibitors, antacids, and H_2-receptor antagonists which increase the gastric pH and may reduce absorption of oral medications including brequinar resulting in decreased systemic exposure. Discontinuation of these medications is not required but is strongly recommended. Ribavirin is to be taken with food (ribavirin generic SPC, Appendix H, Section 15.8).

8.12 TREATMENT COMPLIANCE

Compliance will be assessed by reviewing the subject's medication diary and accounting of returned clinical supplies.

8.13 STORAGE, STABILITY, LABELING AND PACKAGING

8.13.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.13.2 Labeling and Packaging

Each bottle for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-01
Contents: 100 or 250 mg Brequinar capsules
For oral use only. Take with approximately 8 ounces water every 3.5 days.
Subject Number: XX-XXXX
Treatment Duration: As directed
IND: 138355 Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.13.3 Blinding and Randomization

The trial will be conducted in an open-label manner. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist per the

designated mg/m^2 dose for each subject. No randomization codes are necessary for this open-label study.

8.13.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment is known for each subject.

Expectedness will be determined by establishing whether the adverse event is among those identified in the protocol and the Investigator's Brochure or are commonly associated with AML and other hematologic malignancies. The event will be considered expected if commonly associated with these diseases in the opinion of the investigator or Medical Monitor even if not specifically listed in these documents.

8.13.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, used and discarded. It must be clear from the records which subject received which medication. Adequate drug is to be dispensed for each dosing period to allow for dosing every 3.5 days during the period until the next clinic visit, plus one additional dose to act as a spare in the event medication is unable to be used.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

At the end of the study, any unused study drug will be returned to the Sponsor for destruction or destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

8.13.6 Prohibited Medications

Experience with use of ribavirin with interferon in treatment of hepatitis C has concluded that ribavirin should not be given with nucleoside reverse transcriptase inhibitors such as didanosine or with azathioprine. See ribavirin generic SPC, Appendix H Section 15.8.

9 CONDUCT OF THE TRIAL

9.1 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be performed in accordance with the Declaration of Helsinki (1964) (Appendix F) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the ICH Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations.

9.2 INFORMED CONSENT

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50) as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Medicinal Product (IMP), and the hazards involved, as well as the potential benefits that may come from treatment with this IMP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the Food and Drug Administration and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be filed in the Investigator Site File and will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form is attached to this protocol as Appendix E. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes to the sample.

9.3 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEES

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An Investigator's Brochure will be available for review by the IRB. The protocol and consent form must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 SCHEDULE OF EVENTS

Physical examinations, vital signs, ECG, laboratory assessments, bone marrow sampling and other observations will be undertaken by experienced personnel throughout the study based on the

Schedule of Events. Standard chromosomal and mutational testing will be performed per institutional guidelines.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), and lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, platelet count, peripheral blast count, and haptoglobin. Haptoglobin will be assessed pre-dose on the day ribavirin dosing is started, and also one week after starting ribavirin, 4 weeks after starting ribavirin, and one week after adjusting the dose of ribavirin. A haptoglobin result below the lower limit of normal (LLN) for the local laboratory will prompt a discussion with the Medical Monitor, Sponsor, and PI regarding whether the decrease is related to ribavirin use and whether the subject should stop dosing with ribavirin. Haptoglobin should be drawn prior to transfusion of blood products when possible.

In addition to the already scheduled chemistry assessments, subjects taking potentially hepatotoxic drugs are permitted to have more frequent monitoring than indicated in the schedule of events, if ordered by the study team.

9.5 STUDY CONDUCT

9.5.1 Screening Visit (Study Days -14 to -1)

These procedures must be completed within the 14 days prior to starting dosing. Obtain the subject's written informed consent, then collect baseline information:

- Demographics (height, weight, date of birth, gender, race, ethnicity); body surface area (BSA) determined at Screening will be utilized for all BSA-driven mg/m^2 dosing calculations throughout the study.
- Pertinent medical/surgical history (including AML/other hematologic malignancy diagnosis and laboratory and clinical evidence of progression, previous AML/other hematologic malignancy treatment, and any available chromosomal and mutational testing results per institutional guidelines) and concomitant medications.
- Physical examination (including weight).
- Vital signs (heart rate, respiratory rate, seated blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment.
- Hematology/chemistry.
- 12-lead ECG with QTcF.

- Standard chromosomal and mutational testing per institutional guidelines.
- Bone marrow sampling.
- Confirm subject meets all inclusion and no exclusion criteria.

9.5.2 Treatment

The treatment period begins with Cycle 1, Day 1 of the first 2-week dosing cycle. The laboratory manual provides procedures for processing, storage, and shipment of brequinar PK, DHO, and flow cytometry samples. If brequinar PK or DHO levels are not available for dose adjustment decisions, confirm safety is acceptable and continue to dose using the subject's current dosing frequency and current dose until results are available.

9.5.3 Dose Adjustment: Cycle 1 Week 1 (or Week 2 if dose reduced)

Week 1 (or Week 2) Day 1

- Collect any adverse events or new concomitant medications since Screening.
- Collect samples for baseline (pre-dose) brequinar/DHO, flow cytometry, and hematology/chemistry.
- Conduct physical examination (including weight), vital signs, pregnancy test for WOCBP if >4 weeks since last test and 12-lead ECG if >4 weeks since last test.
- Review results and confirm subject remains eligible for the study.
- Dispense study medication.
- Subject is to take the first dose at the clinic and remain for brequinar/DHO/flow cytometry sampling. Collect samples at 1, 2, 4, and 6 hours post dose during Week 1 only.
- Dispense the subject's calendar/diary. The diary will collect dates/times of study medication administration and AEs/new concomitant medications.
- This week's procedures may be repeated for Week 2 if necessary, with the exception that PK/DHO samples are to be obtained pre-dose only on Day 1 of Week 2 in addition to the daily samples on Days 2, 3, and 4.

Week 1 or 2 Day 2:

- Collect 24h post dose brequinar/DHO and flow cytometry samples.

Week 1 or 2 Day 3:

- Collect 48h post dose brequinar/DHO and flow cytometry samples.

Week 1 or 2 Day 4:

- Collect 72h post dose brequinar/DHO samples and flow cytometry samples.

9.5.4 Maintenance Dose Cycle

Once a subject reaches a twice-weekly dose (see Table 8-2 and Figure 8-3), the subject will be in the Maintenance Dose Cycle phase. Each Maintenance Dose Cycle is 2 weeks. The Maintenance Dose Cycle dose may be adjusted at any time using the 84h DHO criteria.

Maintenance Dose Cycle procedures will occur on Day 1 and Day 8 through Week 12 from study Day 1 as shown below. After Week 12, the Maintenance Dose Cycle visit is once every 2 weeks (i.e., Day 1 only of each two-week cycle).

Maintenance Dose Cycle Day 1:

- Collect unused study medication and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect pre-dose brequinar/DHO, hematology/chemistry samples, and flow cytometry sample.
- Obtain vital signs; pregnancy test for WOCBP (every 4 weeks), 12-lead ECG (every 4 weeks), and bone marrow sample (note that bone marrow is collected at the Week 4 visit (Day 22 ±7 days), at the Week 7 visit (Day 43 ±7 days), then every 12 weeks ±7 days or per institutional standard of care; the Day 43 sample will be assessed for hematological toxicity).
- If subject is beginning or continuing twice-weekly dosing, review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and 84h DHO < 1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).
- Dispense study medication (either brequinar alone or brequinar and ribavirin).
- Dispense calendar/diary.

Maintenance Dose Cycle Day 8 (up to Week 12)

- Collect pre-dose brequinar/DHO, and flow cytometry sample.
- Review most recent 84h DHO level, review the laboratory results and safety information and determine whether the subject should maintain current dose (acceptable safety and 84h DHO meets criteria), increase dose (acceptable safety and DHO <1500 ng/mL) or hold study medication (unacceptable safety or 84h DHO ≥ 5000 ng/mL).

9.5.5 Final Visit

This visit is to take place when a subject is discontinuing from the study.

- Collect and check the diary/elicit information about AEs/new concomitant medications since the last visit.
- Collect brequinar/DHO/flow cytometry and hematology/chemistry samples.
- Collect unused study medication.
- Conduct physical examination if >4 weeks since last performed, collect vital signs; conduct pregnancy test for WOCBP if > 4 weeks since previously performed, 12-lead ECG if > 4 weeks since previously performed; collect bone marrow sampling if > 4 weeks since previously performed.
- Ensure all adverse events have been recorded.

9.5.6 Telephone Follow Up Visit (2 weeks after Final Visit)

- Contact subject by telephone two weeks after Final Visit to determine subject's survival status and to inquire if any new adverse events have occurred. Survival information will be collected while the subject is participating in the study (i.e., up to 2 weeks after last dose of study medication).

9.5.7 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final dose.

9.6 COMPLIANCE WITH STUDY PROCEDURES

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol. Provided that activities are carried out within the identified windows, it will not be necessary to file a protocol deviation.

9.7 EARLY WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must be withdrawn from the study if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

9.8 EARLY TERMINATION OF THE STUDY

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor’s request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, **whether or not considered related to the medicinal product.**

Events that occur prior to dosing will be entered as medical history; AEs that occur after dosing will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. AEs will be specified as pre-treatment or treatment-emergent. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Any SAEs experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy, or require changes in study drug (e.g., discontinuation of study drug).

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the End of Study and Death forms.

If a death occurs during the SAE reporting period, the cause of death is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept

on the Adverse Event eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA).

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol-defined visit date.
3. All adverse events will be recorded in the case report form.
4. Serious adverse events will be reported to the IRB according to institutional policy.

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

10.1 CLASSIFICATION OF CAUSALITY

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the PI.

10.2 CLASSIFICATION OF SEVERITY

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm and in Appendix D.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.3 SERIOUS ADVERSE EVENT (SAE) REPORTING

The regulatory definition of a Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect;
- all other events that are considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

Death due to disease progression is considered to be an Expected event in these patients with relapsed/refractory AML/other hematologic malignancy and does not require reporting on an expedited basis.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL OR FAX TO THE SPONSOR CONTACT USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE ECRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address and fax telephone number for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: bpowers@clearcreekbio.com
kumar@clearcreekbio.com

MEDICAL MONITOR: **Vikram Sheel Kumar, MD**
E-mail: kumar@clearcreekbio.com
Telephone: **(617) 899-8944**

Sponsor Representative: **Barbara Powers, MSN, Ph.D.**
E-mail: bpowers@clearcreekbio.com
Telephone: 484-686-0545

All SAEs will be reported to the IRB periodically, at the end of the study or per local institutional guidelines.

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Medical Monitor and site PI. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor is to ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned IRB(s) within seven (7) calendar days of the date of first report to the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the Sponsor.

The Sponsor or designee must also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with additional information requested on an expedited basis.

10.5 PREGNANCIES

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to the Sponsor Contact and to the IRB/IEC by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow-up with the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.6 HEMATOLOGIC ADVERSE EVENTS

It is recognized that laboratory value variability is a frequent and expected and may be present at Baseline when a subject enrolls in the study. In general, mild day to day fluctuation of laboratory values should not be classified as AEs. Fluctuations in laboratory values resulting from adverse changes in the patient's medical condition should be reported as AEs. Laboratory abnormalities that constitute an AE in their own right as per CTCAE V4.03 criteria if applicable (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study drug), should be recorded on the AE eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A laboratory abnormality designated a Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion.

For laboratory abnormalities and any AEs, it should be noted that the terms serious and severe are not symptoms. The term severe describes the intensity of the specific event (e.g., Grade 3 or 4). The term serious is based on patient and event outcomes or actions required as described in the protocol definition of SAEs and is usually associated with events posing a threat to the subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious; laboratory abnormalities (such as WBC or platelet count) may be severe but not serious.

After the subject has completed the first 42 days of treatment, hematologic dose-limiting toxicity (DLT) is defined as prolonged neutropenia with ANC < 500 from the 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 or more. Anemia will not be considered a hematologic AE for the definition of unacceptable safety. The timing of the bone

marrow sampling can be adjusted to ensure that the results are available for the visit on Day 43 (Day 1 of Cycle 4).

Participants with neutropenia or thrombocytopenia because of disease prior to the start of therapy do not require treatment interruption for myelosuppression. Dose reductions of brequinar in these participants should be considered on an individual case basis and discussed with the Sponsor.

10.7 MANAGEMENT OF MYELOSUPPRESSION

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML/other hematologic malignancy. Based on clinical observations with DHODH inhibition and with historical evidence from previous studies with brequinar, participants treated with brequinar may experience thrombocytopenia and neutropenia.

If a participant achieves a clinical response including CR, CRi, CRh, or MLFS while on study and they have not recovered absolute neutrophil count (ANC) > 500/uL within 14 days of study drug interruption, brequinar dosing may be further interrupted until ANC recovers to > 500/uL, unless the low ANC is thought to be due to the underlying disease. Brequinar may be reinitiated at an adjusted dose per discussion with the Sponsor. Granulocyte colony-stimulating factor (GCSF) may be administered if in the best interest of the participant.

10.8 DIFFERENTIATION SYNDROME

Based on its proposed pro-differentiating mechanism of action, it is possible that participants receiving treatment with brequinar may develop signs and symptoms of differentiation syndrome (DS). Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered *per se* as diagnostic of the syndrome, and other causes should be sought and excluded.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation syndrome:

- Temporary hold of brequinar if clinical features cannot be medically managed with the following:
    - Control of leukocytosis with hydroxyurea;
    - Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs,

continued for a minimum of 3 days;

- Initiation of furosemide, if clinically required;
- Prompt initiation of leukapheresis, if required.

If brequinar dosing is held, brequinar may be reinitiated once the participant's clinical condition improves, upon discussion with the Sponsor and Medical Monitor.

10.9 TUMOR LYSIS SYNDROME (TLS)

Tumor lysis syndrome (TLS) is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of hyperkalemia, hyperphosphatemia and hypocalemia associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous extensive clinical experience with brequinar, the experience with brequinar in hematologic malignancies is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). The risk stratification in AML/other hematologic malignancy for TLS from the international guidelines by Cairo et al., 2010 [11] is as follows:

- Low risk disease: WBC < 25 x 10^9 /L and LDH < 2 x upper limit of normal (ULN);
- Intermediate risk disease (IRD): WBC 25 to 100 x 10^9 /L or WBC < 25 x 10^9 /L and LDH ≥ 2 x ULN;
- High risk disease (HRD): WBC ≥ 100 x 10^9 /L.

The guidelines for the prevention, monitoring and treatment of TLS are described below:

TLS Prevention [Recommended]:

- IV hydration: aggressive hydration is recommended for patients at intermediate to high risk for TLS with a goal of initially 2 to 3 L/m^2 per day of IV fluid per the international guidelines (Coiffer et al., 2008 [12]).

- Hypouricemic agents: allopurinol for intermediate risk disease (IRD).

TLS Monitoring: (Howard et al., 2011 [13])

- Figure 10-1 provides a flow chart for TLS monitoring.

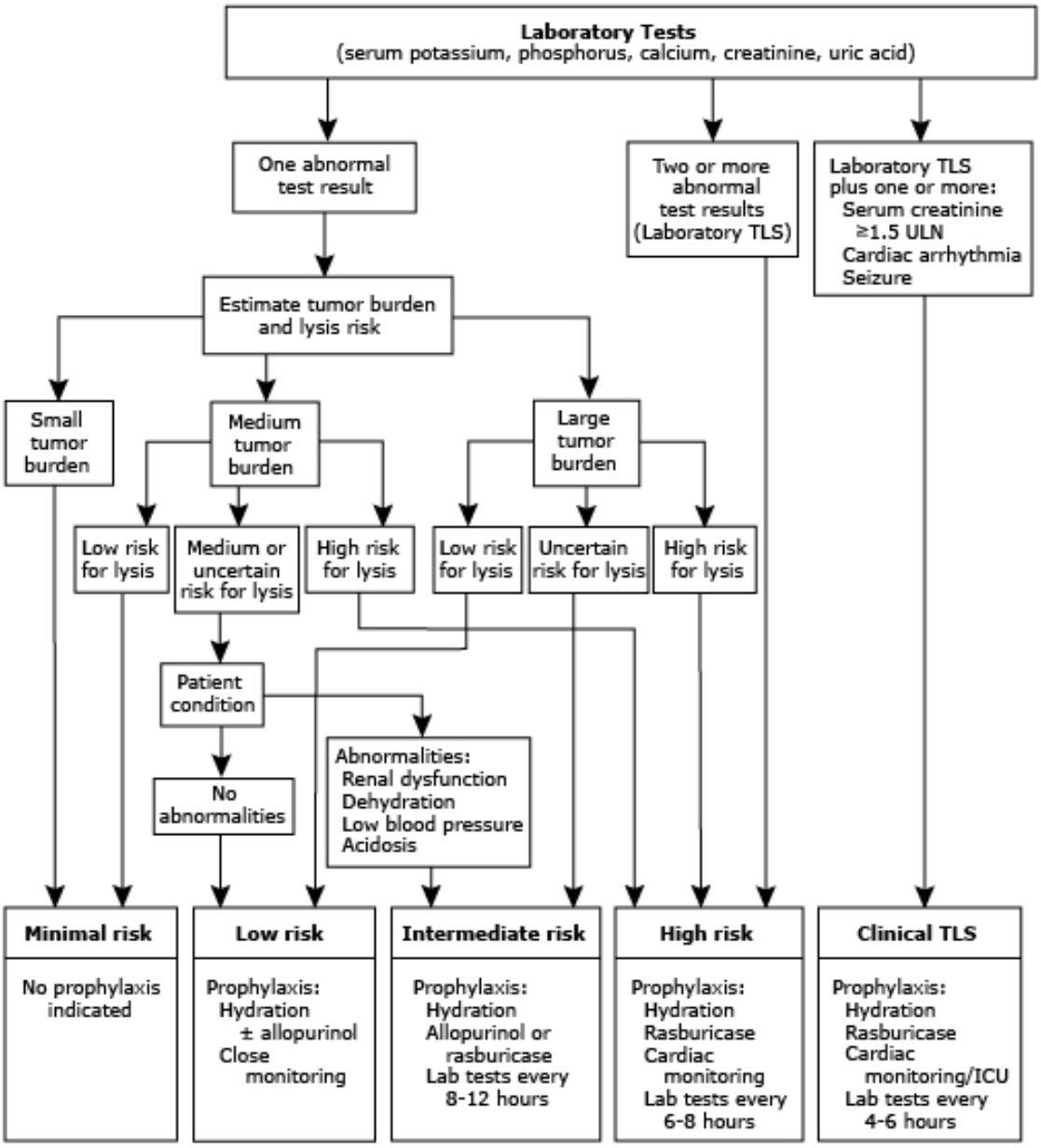

Figure 10-1. Monitoring of Tumor Lysis Syndrome

TLS Treatment

TLS requires urgent inpatient management including intense nursing care, cardiac monitoring, nephrology consultation, and measurements of uric acid, creatinine, and electrolytes every four to six hours. Treat any electrolyte abnormalities and any acute renal injury.

10.10 INFECTION PROPHYLAXIS

Supportive care, including prophylactic antibiotics, antifungal and/or antiviral agents, are frequently used in neutropenic patients, and may be used per standard institutional practice and as deemed necessary by the investigator.

10.11 GROWTH FACTOR SUPPORT

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection, per institutional guidelines.

10.12 MANAGEMENT OF NAUSEA, VOMITING, AND DIARRHEA

Recommended management of nausea and vomiting is to administer antiemetics. The recommended treatment for managing diarrhea is loperamide antidiarrheal therapy, 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. 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 the dose-adjustment phase and the expansion phase. Procedures for accounting for missing, unused and spurious data will be described in the SAP.

Summaries for quantitative variables will include the mean, median, quartiles, standard deviation and error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the exact 95% CI, when appropriate. No hypothesis testing will be performed. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.3 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 STUDY POPULATIONS FOR ANALYSIS

The analysis sets are defined in Table 11-1.

Table 11-1.Analysis Sets

Analysis Set	Description
Enrolled Analysis Set	All subjects who have been enrolled in the study.
Safety Analysis Set	All subjects who were administered brequinar.
Efficacy Analysis Set	All subjects with AML/other hematologic malignancy disease at baseline and who were administered brequinar.
Pharmacokinetic Analysis Set	All subjects who take at least 1 dose of brequinar and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

The Efficacy Analysis Set will be used for efficacy analyses. The Safety Analysis Set will be used for safety analyses.

11.2 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, physical examinations, vital signs, 12-lead ECGs and bone marrow sampling.

Adverse event data will be descriptively evaluated. All AEs will be listed. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 30

days after the last dose of study treatment, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results, vital sign measurements, ECGs and bone marrow assessments will be summarized using appropriate descriptive statistics.

11.3 EFFICACY ANALYSES

Efficacy analyses will be performed using the Efficacy Analysis Set. Table 11-2 summarizes the planned analysis of primary and secondary efficacy endpoints.

Table 11-2.Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	There is no primary efficacy endpoint for this study.
Secondary	• Assess anti-leukemic activity as follows: o Overall Response rate (ORR) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR, CRi, CRh, MLFS and PR o Complete Remission (CR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CR o Complete Remission with Incomplete Hematologic Recovery (CRi) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRi o Complete remission with partial hematological recovery (CRh) – the proportion of subjects in the Efficacy Analysis Set with a best overall response of CRh o Morphologic Leukemia Free State (MLFS) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of MLFS o Partial Remission (PR) rate – the proportion of subjects in the Efficacy Analysis Set with a best overall response of PR o Event-free survival (EFS) – the interval between first brequinar dose and relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death o Overall survival (OS) – the time from first dose of brequinar to date of death or last known alive date For ORR and other endpoints defined as proportions, estimated response rates and two-sided exact binomial 95% CIs will be provided. The distributions of EFS and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Time to event analyses may be performed for the above secondary endpoints from first dose

	of brequinar. Censoring rules for time-to-event endpoints will be described in the SAP.
Exploratory	Will be described in the SAP finalized before database lock.

Disease response for participants with AML/other hematologic malignancy will be assessed based on Döhner et al, 2017 [10].

Complete remission (CR):

- Bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines,
- ANC of at least 1000/µL
- Platelet count of 100,000/µL
- Absence of blasts in peripheral blood
- Absence of identifiable leukemic cells in the bone marrow
- Absence of extramedullary disease.

Complete Remission with Incomplete Blood Count Recovery (CRi):

- Same as for CR but without achievement of ANC at least 1000/uL (CRi) and/or platelet count of 100,000/uL (CRp).

Complete Remission with Partial Hematological Recovery (CRh)

- Complete remission with partial hematological recovery defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter) (Kantarjian HM et al, 2016 [14]).

Partial Remission:

- All hematologic criteria of CR are fulfilled, and
- A decrease of bone marrow blast percentage to 5% to 25%, and
- Decrease of pretreatment bone marrow blast percentage by at least 50%.

Morphologic Leukemia Free State:

- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Stable Disease:

- Failure to achieve a response
- Not meeting criteria for Progressive Disease

Progressive Disease

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/μL), and/or platelet count to >50 x 109/L (50,000/μL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/μl) (in the absence of differentiation syndrome); or
- New extramedullary disease

Duration of Response

- The duration of response is defined as the number of days from the time response criteria are initially met for CR, CRi, CRh, PR, or MLFS (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Clinical Benefit

Requires one of the following in the absence of progression or CR/partial response and independent of marrow response to be considered a clinical benefit:

- Erythroid response

- Transfusion Independence (TI) for ≥ 8 weeks for patients 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 Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.

- Platelet response
  - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks.

Response Criteria in Other Hematologic Malignancies

The criteria used for treatment efficacy in T-ALL and other hematologic malignancies are adapted from Cheson et al., 1990 [25]. In addition to the bone marrow and hematologic criteria above, all previous extramedullary manifestations of disease must be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement). Relapsed disease is defined as the reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (> 5%), in the CNS (positive cytospin examination of cerebrospinal fluid) or in any other extramedullary site after a CR or progression to over 25% leukemia blasts cells in the marrow after a PR.

11.4 OTHER ENDPOINTS

Brequinar Pharmacokinetics (PK) and DHO Levels

Blood samples for brequinar PK and DHO analyses will be obtained at pre-specified times. The following plasma parameters may be analyzed (including but not limited to): concentration maximum (C_{max}), time of peak concentration (T_{max}) elimination half-life ($T_{1/2}$), and area under the concentration curve (AUC) estimated by compartmental and non-compartmental analysis (WinNonlin or similar). Additional parameters may be added as necessary.

Concentration data, PK and DHO parameters will be tabulated and summarized using descriptive statistics. Relationships between brequinar PK parameters and clinical outcomes (e.g., efficacy, toxicity) may be explored. PK analyses will be performed on the PK Analysis Set.

Relationships between DHO levels and PK and clinical outcomes (e.g., efficacy, toxicity) will be explored.

Changes in myeloid markers per serial flow cytometry will be studied to look for evidence of myeloid differentiation.

11.5 SAMPLE SIZE CONSIDERATIONS

Formal sample size calculations are not applicable for this phase 1b/2a, open label study. Up to 27 subjects are planned to be entered in this trial: Cohort 1 had5 subjects; Cohort 2 will have approximately 6 evaluable subjects. Cohort 3 will have approximately 6 evaluable subjects. An expansion cohort of approximately 6 to 12 subjects will be enrolled to further refine brequinar PK and DHO criteria and to further assess the safety, tolerability, and biological activity of brequinar as monotherapy and in combination with ribavirin.

11.6 RANDOMIZATION

No randomization scheme is needed for this open label study.

11.7 POOLING OF STUDY CENTERS

Not applicable to this small, early phase study.

11.8 INTERIM ANALYSIS

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 INVESTIGATOR'S PERFORMANCE

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement (Appendix 15.7) to indicate commitment to comply with the contents.

12.2 CONFIDENTIALITY

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the CRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational medicinal product (IMP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 SOURCE DOCUMENTATION

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IMP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;
- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 DATA COLLECTION

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial.

12.5 CASE REPORT FORMS, INVESTIGATOR'S SITE FILE AND RECORD RETENTION

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the Investigator's Brochure, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IMP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial

correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 NON-PROTOCOL RESEARCH

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 PUBLICATION

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 GENERAL

The Sponsor agrees to adhere to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authority and IRBs.

13.2 INDEMNITY

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 DATA MONITORING

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and Good Clinical Practice obligations, proper maintenance of records including IMP accountability records, correct administration of IMP including storage conditions and accurate reporting of AEs.

Once the data from the case report forms have been entered onto the database, they will be reviewed and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 AUDIT

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 CONFIDENTIALITY

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 FINANCE

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

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15 APPENDICES

15.1 APPENDIX A: CCB-01 SCHEDULE OF EVENTS

CCB-01 Schedule of Events **Procedures[a]**	**Screen[b]**	**Cycle 1 Week 1 or 2**		**Maintenance Dose Cycle**	**Final Visit**	**F/U Phone Call**	**Survival**
		D1	**D2 -D4**	**D1 & D8**		**Final Visit + 2 wks**	
Informed Consent[b]	X						
AE/Concomitant Medications	X	X	X	X	X	X	
Medical history[c]	X						
Demographics[d]	X						
Physical Exam[d]	X	X			X		
Vital Signs[d]	X	X		X	X		
Pregnancy Test (urine or serum)	X			X q 4 weeks	X		
ECOG Performance Status	X						
Hematology/Chemistry[e]	X	X		X (D1 only)	X		
Chromosomal/mutational testing[f]	X						
12-lead ECG	X			X q 4 weeks	X		
Bone Marrow Sampling[g, h]	X			X q 12 weeks	X		
Biobanking samples[g]	X			X	X		
Brequinar/DHO/Flow Cytometry Sample[h]		X	X	X	X		
Ship DHO Plasma Samples[i]			X (D4)	X	X		
Dispense/Collect Study Medication		X		X	X		
Dispense/Collect Subject Calendar/Diary		X		X	X		
Survival Assessment							X

a. Visit window of ± 1 day for Cycle 1 visits; window of ± 3 days for Maintenance Dose cycles.
b. Obtain informed consent prior to performing any screening or study-specific procedures. Screening procedures must be performed within 14 days prior to initial study drug administration. Procedures at C1D1 that are repeats of Screening may be omitted if <1 week since Screening assessment. ECG and pregnancy test frequency are every 4 weeks or per institutional guidelines.
c. Medical history is to include AML/other hematologic malignancy diagnosis, previous AML/other hematologic malignancy treatment, and standard chromosomal and mutational results per institutional guidelines.
d. Demographic information is to include date of birth, height, weight, race, and ethnic origin. Rectal examination may be deferred for Physical Examination. Vital signs include heart rate, respiratory rate, seated blood pressure, respiratory rate, oral/aural body temperature. Complete physical examination and vital signs once every 4 weeks or more often if needed to assess an AE.
e. If additional complete blood count (CBC) with differential results are available (for example, daily reports when a subject is hospitalized), these results may be captured in the eCRF using an Unscheduled visit.
f. Testing panel is per institutional standard of care; obtain sample at Screening.
g. Bone marrow sampling local testing will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. Local molecular analysis will be performed on the screening bone marrow samples only. Bone marrow samples will be sent for biobanking for possible further analysis from Screening, Week 7 (Day 43), and Final Visit. Perform bone marrow sampling at screening, at Visit 4 (Day 22), Visit 7 (Day 43), then once every 12 weeks. Timing of this procedure may be adjusted to ensure results are available for the next clinic visit. Procedure window is ±7 days.
h. Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.
i. Process, store and ship these samples per the Laboratory Manual.
j. Cycle 1 Week 1 procedures are to be repeated for Week 2 if starting dose was decreased to 200 mg/m^2 or dose held until a twice-weekly dose has been determined with the exception that PK/DHO/Flow samples will be obtained only once per day in Week 2.

15.2 APPENDIX B: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal level. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal level; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous level, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal level with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal level or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15.3 APPENDIX C: BREQUINAR/DHO/FLOW CYTOMETRY SAMPLING

Information is provided in a separate laboratory manual regarding collection, processing, storing, and shipment of samples.

Cycle 1 Day 1 sample window ±15 minutes through 6h draw; window for additional C1 draws ±2h; window for Dose Adjustment Week plasma brequinar/DHO draws ±2h; window for Maintenance Cycle samples is ±4h. Ensure 84h DHO trough samples (~84 hours after most recent dose) are obtained prior to dosing.

Brequinar and DHO plasma samples and peripheral blood for flow cytometry are to be obtained at the following time points:

	Cycle 1 Week 1 (or 2)							
	D1					D2	D 3	D 4
Time Point	Pre-dose	1h*	2h*	4h*	6h*	24h	48h	72h
*These time points to be obtained in Week 1 only.								

	Maintenance Cycle **(Day 8 through Week 12 only)**	
	D1	D8
Time Point	Pre-dose ~84h after previous dose	Pre-dose ~84h after previous dose

15.4 APPENDIX D: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

15.5 APPENDIX E: SAMPLE SUBJECT CONSENT FORM

TITLE: A Phase 1b/IIa 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)

PROTOCOL NO.: CCB-01

SPONSOR: Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

INVESTIGATOR: <insert PI name>
Site(s): <insert name>
<insert address>

STUDY-RELATED PHONE NUMBER(S): <insert name(s)>
<insert number>
<insert alternate number (24-hour contact number)>

VERSION and DATE: <e.g. CCB-01 Master ICF Version 4.0 21 February 2020>

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish, before deciding whether or not to take part. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to evaluate the safety, efficacy, pharmacokinetics (PK) (level of study medication in the blood) and the inhibition (decrease in level) of an enzyme called "dihydroorotate dehydrogenase" (DHODH). DHODH blocks the ability of blood cells formed in the bone marrow to differentiate (grow into mature white blood cells that can fight infection and platelets that help blood to clot). Brequinar is a drug that has been shown in animals in the laboratory to be able to decrease the level of DHODH and decrease leukemic cells in the bone marrow. Reducing DHODH level in patients with AML/other hematologic malignancy may help treat this type of leukemia by allowing cells in the bone marrow to grow into different types of mature cells. After brequinar has been shown to be safe and well tolerated when given to you, another drug called ribavirin will be added as a combination treatment.

WHY HAVE I BEEN ASKED TO PARTICIPATE?

You have been asked to consider participating in this study because you because you have AML/other hematologic malignancy that has not responded to treatment (refractory), or the leukemia has recurred (relapsed).

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will last approximately 7 - 12 months and approximately 27 subjects will be participating in this study. If you respond (your leukemia improves) due to the effects of the study medication, you may be able to continue being treated for up to one year. You will begin the study by taking the study medication once a week for at least the first week. After the results of certain blood tests are known (level of study drug and the enzyme being tracked in this study), the dose may be adjusted and your schedule may be changed to twice-weekly or about every three-and-one-half (3.5) days, for example on Monday mornings and Thursday evenings for the remainder of the time you are participating in the study. You and your study team can decide on the exact schedule for you to take your medication.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in the study, you will have the following procedures:

Screening Assessment

The Screening period is defined as the period prior to the administration of study drug. During this period, the investigator or designee will obtain/perform the following:

- Written, informed consent;
- Demographic details (height, weight, date of birth, race, ethnicity).
- Pertinent medical/surgical history, medications you are currently taking or have taken recently.
- Physical examination.
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature).
- Pregnancy test for women of childbearing potential (WOCBP).
- ECOG performance assessment (a measure of your ability to perform activities of daily living).
- Blood samples for hematology/chemistry.
- Standard chromosomal and mutational testing (blood samples) if not already done.
- Bone marrow sampling (aspiration and biopsy).
- 12-lead ECG with QTcF to assess cardiac function.

If you qualify for the study, the treatment period begins with Cycle 1, Day 1 of the first dosing cycle.

Cycle 1 Week 1 (also Cycle 1 Week 2 if dose reduced after Week 1 dosing)

- **Week 1 (or Week 2) Day 1:**

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination (including weight) (unless within one week of Screening), vital signs, pregnancy test for women able to bear children, and 12-lead ECG.
- If you qualify for the study and choose to participate, you will be given study medication to take while at this clinic visit.
- You will take the first dose at the clinic and remain at the clinic for pharmacokinetic (PK) and dihydroorotate (DHO) blood sampling at 1, 2, 4, and 6 hours after this first dose. Each dose of study medication will be made up of several capsules, depending on what dose you will be taking. Take the medication with about 8 ounces of plain water. You can take more water than 8 ounces if needed.
- Be given a calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

- **Week 1 (or 2) Day 2**: You will come back to the clinic approximately 24 hours (the next day) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 (or 2) Day 3**: You will come back to the clinic approximately 48 hours (2 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.
- **Week 1 (or 2) Day 4**: You will come back to the clinic approximately 72 hours (3 days) after your first dose to have blood samples taken for brequinar/DHO and flow cytometry.

Maintenance Dose Cycle (visit every week up to Week 12 then every 2 weeks)

Once you reach a twice-weekly dose, you will be in the Maintenance Dose Cycle.

In the first 12 weeks from starting study drug (after finding twice-weekly dosing), the Maintenance Dose Cycle procedures will occur every week on Day 1 and Day 8. After completing 12 weeks from starting study drug, you may come to the clinic for a Maintenance Dose Cycle visit once every 2 weeks (Day 1 only).

Maintenance Dose Cycle Day 1:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.
- Have a physical examination every 4 weeks (including weight) (unless within one week of Screening), vital signs, pregnancy test for women able to bear children once every 4 weeks, a 12-lead ECG once every 4 weeks, and a bone marrow sample every 12 weeks.
- Take the first dose of the week at the clinic; if you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week; if beyond Week 12, adequate medication will be provided for the entire two-week cycle.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.

Maintenance Dose Cycle Day 8:

At this visit you will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, and flow cytometry.
- Take the first dose of the week at the clinic.
- If you have moved to twice-weekly dosing, you will be given adequate study medication for the second dose of the week to be taken 3.5 days after the first dose of the week.
- Be given a new calendar/diary you will use to write down the dates/times of study medication administration and any new medical events, new medications or a change in dose of any medications. Please bring your study medication and diary to every visit.
- You will not need to have this visit after Week 12.

Final Visit

This visit is to take place when you are leaving the study. You will:

- Be asked about any new medical events or new or changed medications since your last visit.
- Have blood samples taken for baseline brequinar/DHO, flow cytometry, and hematology/chemistry.

- Have a physical examination (including weight), vital signs, pregnancy test for women able to bear children if more than 4 weeks since the last test, 12-lead ECG if more than 4 weeks since the last test, and bone marrow sample if more than 4 weeks since the last test.
- Any leftover study medication will be collected.
- Your diary will be checked for any new medical events, new medications or a change in dose of any medications.

Telephone Follow Up Visit (2 weeks after Final Visit)

- You will be contacted by telephone approximately two weeks after Final Visit to inquire if any new adverse events have occurred. Survival information will be collected while you are participating in the study (i.e., up to 2 weeks after last dose of study medication).

Unscheduled Visits

You may ask to come to the clinic when needed to be seen for unscheduled visits and tests to assess any new medical events providing the onset occurs within two (2) weeks after you have taken the final dose of study medication.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART IN THIS RESEARCH?

Risks from brequinar:

While participating in this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form.

Brequinar has been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patient with psoriasis (a skin condition) and those who have had a kidney or liver transplant. The most common side effects have been:

- Thrombocytopenia/hemorrhage (low platelet count, platelets are a part of the blood that help your blood clot, they may need to be replaced)
- Stomatitis/mucositis (the inside of your mouth and intestines may develop ulcers which make eating and drinking difficult)
- Skin rash
- Nausea
- Vomiting
- Diarrhea

- Neutropenia (low white blood cell count, which may reduce the body's ability to fight infections)
- Infections
- Anemia (low red blood cell count, red cells carry oxygen)
- Fatigue

Some of these side effects were severe enough in patients treated with brequinar to require hospitalization or caused death. In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar, but that cannot be guaranteed as the drug may work differently for you. If you develop these side effects during the study, your study team may decide to have you temporarily stop taking brequinar to see if the side effects get better. You and your study team may also decide to either stop your study participation or reduce the dose of the study medication to see if you can tolerate a lower dose.

Brequinar may cause a condition called differentiation syndrome. This is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has not been previously seen with brequinar. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs, around the neck, groin, or underarm area
- Fast weight gain (more than 10 pounds within a week)
- Bone pain

If you develop differentiation syndrome, your healthcare provider may start you on corticosteroids which you will either take by mouth or receive by vein. You may be monitored in the hospital.

You may also develop Tumor Lysis Syndrome (TLS). TLS is characterized by nausea, vomiting, diarrhea, anorexia, lethargy, irregular heart rhythms, heart failure, hematuria, seizures, muscle cramps, syncope, tetany and possible sudden death due to the acute metabolic irregularities of low blood levels of potassium, phosphorous, and calcium associated with the breakdown of tumor cells secondary to cytotoxic therapy.

While TLS was not observed in the previous subjects who took brequinar in a clinical trial, the experience with brequinar in AML/other hematologic malignancy is limited. Signs and symptoms of TLS will therefore be carefully monitored particularly in the period that tumor lysis is most likely to occur (24-48 hours after first dose). If you develop this condition, you will be carefully monitored and may need to be treated in the hospital.

Risks from Ribavirin

Ribavirin is marketed for treatment of hepatitis C but will be used in this study as an anti-cancer medication. Risks commonly associated with ribavirin administration in adult patients receiving ribavirin included:

- fatigue/asthenia
- headache, rigors
- fevers
- nausea
- myalgia
- anxiety/emotional lability/irritability
- hemolytic anemia

Risks from Study Procedures:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow sampling** (biopsies and aspirations) performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Bone marrow sampling will include analysis of the aspirate on smear, core biopsy by microscopy, flow cytometry, and karyotype for cytogenetics. You can talk with the study team about this testing. The type of genetic testing being performed for this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

There may be risks or side effects that are unknown at this time.

If a condition of which you were unaware is discovered during the study, a full report will be sent to your doctor if you request this. You will be advised of the appropriate action to take for treatment.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while participating in this study. If you are able to become pregnant or father a child, you must use birth control during the study and for at least 3 months after your last dose of study drug if you are sexually active.

Birth control specifications: Female participants who are able to become pregnant must use 2 methods of birth control while on this study. Male participants must use an effective barrier method (such as a condom) while on this study.

Talk with the study team about acceptable methods of birth control to use while taking part in this study.

Males: Tell the study team right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled into this study. If you become pregnant or suspect that you are pregnant during the study, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

WHAT ARE THE POSSIBLE BENEFITS?

Either or both or the combination of the study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

WILL IT COST ANYTHING TO BE IN THE STUDY?

If you participate in this study, you will not have to pay for the cost of the study drug used in the study.

You or your insurer will be responsible for the cost of your usual ongoing medical care, including procedures and non-study medications that the doctor or your regular doctor requires during this study as part of your usual medical care. If you have any questions, please ask the doctor and/or a member of the study staff about the costs that will or will not be covered by the sponsor.

IS THERE PAYMENT FOR PARTICIPATION?

You will not receive any payment for participation in this study.

WHAT ARE THE ALTERNATIVES FOR TREATMENT?

You do not have to participate in this research study to receive treatment. Instead, you may be eligible for recently approved therapies, and may be able to have a bone marrow transplant outside of this study. You may choose to receive other investigational therapies, if available. You may also choose not to have treatment for cancer at all. Regardless of your choices, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer. Please note that you will be informed in a timely manner if new information becomes available that is relevant during your participation in this study.

WHAT IF SOMETHING GOES WRONG?

An important part of this study is to see if the investigational product causes side effects. You must inform the staff if you feel unwell or have any unusual symptoms at any time during the study, no matter how minor you think they are. If you experience such events, treatment will be made available by the doctor.

You will be provided any reasonably necessary medical treatment for any injuries sustained as a result of participating in this study, except to the extent such costs are covered by your medical or hospital insurance or by governmental programs providing such coverage. You must follow the directions of the doctor to be eligible for this coverage. Neither the sponsor nor the doctor have plans to provide other compensation in the event of an injury. You are not giving up any of your legal rights by signing this consent form.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

WILL ALL THE DOCUMENTS CONCERNING ME REMAIN CONFIDENTIAL?

Yes. The company that is conducting this study will not keep any document on file that contains your name; you will only be identified by your initials and a subject number. It will be necessary for the sponsor, its representatives, the regulatory authorities, other institutions participating in the study, and possibly the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study) to review your medical records, but these will be treated in the strictest confidence permitted by law. If the results of the study are published, you will not be identified by name. Your personal health information (PHI) will be kept as confidentially as possible according to state and federal laws. However, in some situations, the Food and Drug Administration (FDA) could be required to reveal the names of participants.

The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

This section explains how your medical and health records might be used and shared if you agree to participate in this study. If you do not sign this consent form, you cannot participate in the study.

During the study, the doctor and/or a member of the study staff will record health information about you (your "records"). Your records include the data collected or reviewed during the study, including data about the physical examination, tests, and other procedures described above. Your records also will include identifying information, such as your name and address.

By signing this consent form, you:

- Allow the doctor and/or a member of the study staff to use your records to carry out this study.

- Allow the doctor and/or a member of the study staff to share your records with the company paying for this study, Clear Creek Bio, Inc., their representatives, and other researchers involved in this study. These people will use these records to review the study and to check the safety of the study.

- Allow the doctor or sponsor to publish results of the study in medical journals or to present results at meetings. If this happens, your name will not be used. The doctor also may share all of your records and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA), and government agencies in other countries. They may also share your records with regulatory agencies. These agencies may use these records to check the information collected in this study, to check how the study is carried out, and to check subjects' safety.

There are national and state laws that state that the doctor must protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information as described above. After the doctor shares your records with the sponsor and others, the laws may no longer protect the privacy of your records. These records might be shared with other people who do not have to protect the privacy of your records.

If you get hurt or sick possibly because of being in the study, and you seek medical treatment:

- The doctor and sponsor may obtain study-related records from your or other health care providers to learn more about the effects of the study and your condition.

- Information about this study might be given to your insurance company or health care payer for the purpose of resolving your claim.

- The sponsor might give information that identifies you to its insurance carrier for the purpose of resolving your insurance claim.

You have the right to see and copy your records in the doctor's possession. However, by signing this consent form, you agree that you might not be able to review some of these records related to

the study until after the study is complete. At that time, your right to see these records will be restored.

This consent form has no expiration date. If you do not cancel this consent form, then it will remain valid indefinitely.

You will receive a signed and dated copy of this consent for your records.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be reported in a Clinical Study Report and may be published in scientific journals or presented in scientific meetings. The results of this study may also be used to support regulatory filings by the sponsor in support of the use of this medication for treating AML/other hematologic malignancy or other blood cancers or diseases. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO IS ORGANIZING AND FUNDING THE RESEARCH?

The study has been organized and funded by Clear Creek Bio, Inc. The investigational medicinal product (study drug) is being provided by Clear Creek Bio, Inc.

DO I HAVE TO TAKE PART?

Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you decide to take part, you will be asked to sign and date this consent form and given a copy to keep.

Your participation in this study may be ended by the doctor, sponsor, the regulatory agencies or the Institutional Review Board (an IRB is a group of people who review the risks and benefits of a study). They can end your participation for any of the following reasons without your consent:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If this is the case, you will be given further instructions by the doctor for any final evaluations that may be needed.

CONTACT FOR FURTHER INFORMATION

Any questions, concerns, or complaints about this study or if you feel you have had a research-related injury or reaction to the study drug should be directed to <insert PI name and contact information [24-hour contact]>.

If you have questions about your rights as a research subject or for questions, concerns or complaints about the research, you may contact:

<Insert IRB name >

<Insert address>

<Insert telephone number>

<Insert email if applicable>

The IRB will not be able to answer some study-specific questions however, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will be given a signed and dated copy of this consent form to keep.

Thank you for taking the time to read this consent form.

Consent Form Signature Page

SUBJECT'S DATE OF BIRTH: _____/_____/_____

mmm / dd / yyyy

Print Name of Investigator:_____

	Please initial box:
1. I confirm that I have read this consent form for the above study and have had the opportunity to ask questions.	
2. I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical records may be looked at by responsible individuals from Clear Creek Bio, Inc. and/or its representatives or from regulatory authorities and the IRB where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I understand that my data may be transmitted outside the country to countries with less strict data protection laws.	
5. I agree to take part in the above study.	

By signing this consent form, I have not given up any of my legal rights.

_____	_____	_____	_____
Printed Name of Subject	Signature of Subject	Date	**Time**
_____	_____	_____	_____
Printed Name of person conducting informed consent discussion	Sign	Date	**Time**

Original with Investigator File 1 copy for subject 1 copy for Subject's Medical Records

15.6 APPENDIX F: WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized

representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

15.7 APPENDIX G: INVESTIGATOR'S STATEMENT AND AGREEMENT

STUDY NUMBER: CCB-01

STUDY TITLE: 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)

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

Site Address:

_____

_____

_____

_____

15.8 APPENDIX H: RIBAVIRIN GENERIC (RIBAVIRIN USP) CAPSULES, FOR ORAL USE SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

PACKAGE LEAFLET: INFORMATION FOR THE USER
Ribavirin Aurobindo 200 mg capsules, hard
Ribavirin

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT RIBAVIRIN AUROBINDO IS AND WHAT IT IS USED FOR

Ribavirin Aurobindo contain the active ingredient ribavirin. Ribavirin Aurobindo stops the multiplication of many types of viruses, including hepatitis C virus. Ribavirin Aurobindo must not be used without interferon alfa-2b, i.e. Ribavirin Aurobindo must not be used alone.

Previously untreated patients:
The combination of Ribavirin Aurobindo with interferon alfa-2b is used to treat patients 3 years of age and older who have chronic hepatitis C (HCV) infection. For children and adolescents weighing less than 47 kg a solution formulation is available.

Previously treated adult patients:
The combination of Ribavirin Aurobindo with interferon alfa-2b is used to treat adult patients with chronic hepatitis C, who have previously responded to treatment with an alfa interferon alone, but whose condition has recurred.

There is no safety or efficacy information on the use of Ribavirin Aurobindo with pegylated or other forms of interferon (i.e., not alfa-2b).

2. BEFORE YOU TAKE RIBAVIRIN AUROBINDO

Ribavirin Aurobindo is not recommended for use in patients under the age of 3 years.

DO NOT take Ribavirin Aurobindo
If any of the following apply to you or your child you are caring for, **do not take** Ribavirin Aurobindo, and **tell your doctor** if you:

- are **allergic** (hypersensitive) to ribavirin or any of the other ingredients of Ribavirin Aurobindo capsules (see section 6, further information).
- are **pregnant or planning to become pregnant**. (see section “pregnancy and breast-feeding).
- are **breast-feeding**.
- have had any previous severe heart problem, or have had any problems with the **heart** in the last 6 months
- have any severe medical conditions that leave you very weak, including severe kidney disease.

- have severe **kidney** disease and/or are on haemodialysis
- have had severe **liver** problems, which are not related to hepatitis C.
- have suffered from any **blood disorder**, for example anaemia (low blood count), thalassemia or sickle-cell anaemia.
- Have suffered from autoimmune disease in the past, or suffer from autoimmune hepatitis or are taking other medicine that suppress your immune system (that protects you against infection and some diseases).

Children and adolescents must not take combination therapy with Ribavirin Aurobindo and alpha interferon when there is existence or history of serious nervous or mental problems, such as severe depression, suicidal thoughts or attempted suicide.

You should tell your doctor if you have suffered from any other serious illness in the past.

- Reminder: Please read the "Do not use" section of the package leaflet for interferon alfa-2b before you begin combination treatment with Ribavirin Aurobindo.

Take special care with Ribavirin Aurobindo
- Seek medical advice **immediately** if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while taking this treatment.

Children and adolescents weighing less than 47 kg:
The use of Ribavirin Aurobindo is not recommended.

You should **tell your doctor** if you or your child you are caring for:
- are an adult who has or had a severe **nervous or mental disorder**, confusion, unconsciousness, or have had **thoughts of suicide** or **have attempted suicide,** or have a **history of substance abuse** (e.g. alcohol or drugs)
- have ever had **depression** or develop symptoms associated with depression (e.g. feeling of sadness, dejection, etc.) while on treatment with Ribavirin .
- are a woman of **childbearing** age (see section "Pregnancy and breast-feeding")
- are a **male** and your female partner is of childbearing age (see section "Pregnancy and breastfeeding")
- had a previous serious **heart** condition or have cardiac disease
- are older than **65 years** or if you have problems with your **kidneys**
- have or have had any **serious illness**
- have **thyroid** problems

During treatment with Ribavirin Aurobindo in combination therapy with an alfa interferon, **dental and gum disorders**, which may lead to loss of teeth, have been reported. In addition, **dry mouth** that could have a damaging effect on teeth and membranes of the mouth has been reported during longterm treatment with ribavirin in combination therapy with an alpha interferon. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience **vomiting**. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During treatment with Ribavirin Aurobindo in combination therapy with an alpha interferon, patients may experience **eye problems,** or loss of vision in rare instances. If you receive ribavirin in combination with an alpha interferon, you should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting eye disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic eye exams during combination therapy with ribavirin and an alpha interferon. Combination therapy with ribavirin and an alpha interferon should be discontinued in patients who develop new or worsening eye disorders.

- Reminder: Please read the "Take special care" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Taking other medicines

Please tell your doctor or pharmacist if you or the child you are caring for:
- are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- are receiving azathioprine in combination with ribavirin and pegylated alpha interferons and, therefore may be at an increased risk of developing severe blood disorders.
- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicinal product(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]:
    - Taking Ribavirin Aurobindo in combination with an alpha interferon and an anti-HIV medicinal product(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).
    - With **zidovudine** or **stavudine**, it is not certain if ribavirin will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your Ribavirin Aurobindo treatment needs to be changed. Additionally, patients receiving **zidovudine** with **ribavirin** in combination **with alpha interferons** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine and ribavirin in combination with alpha interferons is not recommended.
    - Due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis, the use of **ribavirin and didanosine** is not recommended and the use of **ribavirin and stavudine** should be avoided.
    - Co-infected patients with advanced liver disease receiving (HAART) may be at increased risk of worsening liver function. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Reminder: Please read the "Taking other medicines" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Taking Ribavirin Aurobindo with food and drink
Ribavirin Aurobindo must be taken with food.

Pregnancy and breast-feeding
If you are **pregnant** you must not take Ribavirin Aurobindo. Ribavirin Aurobindo can be very damaging to your unborn baby (embryo).

Both female and male patients must take **special precautions** in their sexual activity if there is any possibility for pregnancy to occur:

- **Girl** or **woman** of childbearing age:

You must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This should be discussed with your doctor.

- **Men:**

Do not have sex with a pregnant woman unless you **use a condom**. This will lessen the possibility for ribavirin to be left in the woman's body.
If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for 7 months after treatment has stopped. You or your female partner must use an effective contraceptive during the time you are taking Ribavirin

Aurobindo and for 7 months after stopping the treatment. This should be discussed with your doctor (see section "Do not take Ribavirin Aurobindo").

If you are a woman who is **breast-feeding**, you must not take Ribavirin Aurobindo. Discontinue breastfeeding before starting to take Ribavirin Aurobindo.

Driving and using machines
Ribavirin Aurobindo has no effect on your ability to drive or use machines. However, interferon alfa-2b may cause sleepiness, tiredness or confusion.
Do not drive or use any tools or machines if you feel tired or sleepy, or are confused.

Important information about some of the ingredients of Ribavirin Aurobindo
Each Ribavirin Aurobindo capsule contains a small amount of **lactose**. If you have been told by your doctor that you have **an intolerance to some sugars**, discuss with your doctor before taking this medicinal product.

3. HOW TO TAKE RIBAVIRIN AUROBINDO

General information about taking Ribavirin Aurobindo
If the child you are caring for is **under the age of 3 years**, do not administer.

Always take Ribavirin Aurobindo exactly as your doctor has told you. You should check with your doctor or pharmacist, if you are not sure.

Do not take more than the recommended dosage and take the medicine for as long as prescribed. Your doctor has determined the correct dose of Ribavirin Aurobindo based on how much you or the child you are caring for weighs..

Standard blood tests will be taken to check your blood, kidney and liver function.
- Blood tests will be done regularly to help your doctor to know if this treatment is working.
- Depending upon the results of these tests, your doctor may change/adjust the number of hard capsules you or the child you are caring for take, prescribe a different pack size of Ribavirin Aurobindo, and/or change the length of time to take this treatment.
- If you have or develop severe kidney or liver problems, this treatment will be stopped.

The usual dose, according to how much the patient weighs, is shown in the table below:
1. Look for the line that shows how much the adult or child/adolescent weighs.
   Reminder: If the child is under the age of 3 years, do not administer.
2. Read across on the same line to see how many hard capsules to take.
   Reminder: If your doctor's instructions are different from the amounts in the below table, follow your doctor's instructions.
3. If you have any questions about the dose, ask your doctor.

Ribavirin Aurobindo for oral use - dose based on body weight		
If the **adult** weighs (kg)	Usual daily Ribavirin Aurobindo dose	Number of 200 mg capsules
< 65	800 mg	2 capsules in the morning and 2 capsules in the evening
65 – 80	1,000 mg	2 capsules in the morning and 3 capsules in the evening
81 - 105	1,200 mg	3 capsules in the morning and 3 capsules in the evening
> 105	1,400 mg	3 capsules in the morning and 4 capsules in the evening

If the **child/adolescent** weighs (kg)	Usual daily Ribavirin Aurobindo dose	Number of 200 mg capsules
47 – 49	600 mg	1 capsule in the morning and 2 capsules in the evening
50 – 65	800 mg	2 capsules in the morning and 2 capsules in the evening
> 65	see adult dose and corresponding number of hard capsules	

Take your prescribed dose by mouth with water and during your meal. Do not chew the hard capsules. For children or adolescents who cannot swallow a hard capsule, an oral solution of ribavirin is available.

Reminder: Ribavirin Aurobindo is only to be used in combination with interferon alfa-2b or hepatitis C virus infection. For complete information be sure to read the "How to use" section of the Package Leaflet for interferon alfa-2b.

Interferon medicine that is used in combination with Ribavirin Aurobindo may cause unusual tiredness; if you are injecting this medicine yourself or giving it to a child, use it at bedtime.

If you take more Ribavirin Aurobindo than you should
Tell your doctor or pharmacist as soon as possible.

If you forget to take Ribavirin Aurobindo
If you are self-administering treatment, or if you are the caregiver of a child taking Ribavirin Aurobindo in combination with interferon alfa-2b, take/administer the missed dose as soon as possible during the same day. If an entire day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Please read the "Possible side effects" section of the Package Leaflet for interferon alfa-2b.

Like all medicines, Ribavirin Aurobindo used in combination with an alpha interferon product can cause side effects. although not everybody gets them.

Psychiatric and Central Nervous System:
Some people get depressed when taking ribavirin in combination treatment with an interferon, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with ribavirin and interferon alpha. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with ribavirin, in combination with interferon alfa-2b, some children and adolescentsdid not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Contact your doctor immediately if any of the following side effects occur during treatment with Ribavirin Aurobindo in combination with an alpha interferon product:

- chest pain or persistent cough
- changes in the way your heart beats
- fainting
- confusion,
- feeling depressed
- suicidal thoughts or aggressive behaviour,
- attempt suicide,
- thoughts about threatening the life of others,
- feelings of numbness or tingling
- trouble sleeping, thinking or concentrating
- severe stomach pain
- black or tar-like stools
- blood in stool or urine
- severe bleeding from your nose
- fever or chills beginning after a few weeks of treatment
- lower back or side pain
- painful or difficult urination
- problems with your eyesight or hearing**,**
- severe skin rash or redness

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)
Not known (frequency cannot be estimated from the available data).
The following side effects have been reported with the combination of ribavirin and an alpha interferon product **in adults**:

Very commonly reported side effects:

- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in neutrophils (that make you more susceptible to different infections).
- difficulty concentrating, feeling anxious or nervous, mood swings, feeling depressed or irritable, tired feeling, trouble falling asleep or staying asleep,
- cough, dry mouth, pharyngitis (sore throat)
- diarrhoea, dizziness, fever, flu-like symptoms, headache, nausea, shaking chills, virus infection, vomiting, weakness,
- loss of appetite, loss of weight, stomach pain,
- dry skin, irritation, pain or redness at the site of injection, hair loss, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Commonly reported side effects:

- decrease in blood clotting cells called platelets that may result in easy bruising and spontaneous bleeding, decrease in certain white blood cells called lymphocytes that help fight infection, decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms) excess of sugar or uric acid (as in gout) in the blood, low calcium level in the blood, severe anaemia
- fungal or bacterial infections, crying, agitation, amnesia, memory impaired, nervousness, abnormal behaviour, aggressive behaviour, anger, feeling confused, lack of interest, mental disorder, mood changes, unusual dreams, wanting to harm yourself, feeling sleepy, trouble sleeping, lack of interest in sex or inability to perform, vertigo (spinning feeling)
- blurred or abnormal vision, eye irritation or pain or infection, dry or teary eyes, changes in your hearing or voice, ringing in ears, ear infection, earache, cold sores (herpes simplex), change in taste, taste loss, bleeding gums or sores in mouth, burning sensation on tongue, sore tongue, inflamed gums, tooth problem, migraine, respiratory infections, sinusitis, nose bleed, nonproductive cough, rapid or difficult breathing, stuffy or runny nose, thirst, tooth disorder,

- cardiac murmur (abnormal heart beat sounds), chest pain or discomfort, feeling faint, feeling unwell, flushing, increased sweating, heat intolerance and excessive sweating, low or high blood pressure, palpitations (pounding heart beat), rapid heart rate.
- bloating, constipation, indigestion intestinal gas (flatus), increased appetite, irritated colon, irritation of prostate gland, jaundice (yellow skin), loose stools, pain on the right side around your ribs, enlarged liver, stomach upset, frequent need to urinate, passing more urine than usual, urinary tract infection, abnormal urine,
- difficult, irregular, or no menstrual period, abnormally heavy and prolonged menstrual periods, painful menstruation, disorder of ovary or vagina, breast pain, erectile problem,
- abnormal hair texture, acne, arthritis, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions),hives, increased or decreased sensitivity to touch, nail disorder, muscle spasms, numbness or tingling feeling, limb pain, pain at the site of injection, pain in joints, shaky hands, psoriasis, puffy or swollen hands and ankles, sensitivity to sunlight, rash with raised spotted lesions, , redness of skin or skin disorder, swollen face, swollen glands (swollen lymph nodes), tense muscles, tumour (unspecified), unsteady when walking, water impairment.

Uncommonly reported side effects:
- hearing or seeing images that are not present,
- heart attack, panic attack,
- hypersensitivity reaction to the medication,
- inflammation of pancreas, pain in bone, diabetes mellitus,
- muscle weakness.

Rarely reported side effects:
- seizure (convulsions)
- pneumonia,
- diabetes, rheumatoid arthritis, kidney problems,
- dark or bloody stools, intense abdominal pain
- sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands),
- vasculitis.

Very rarely reported side effects:
- suicide.
- stroke (cerebrovascular events)

Not known side effects:
- thoughts about threatening the life of others,
- mania (excessive or unreasonable enthusiasm),
- pericarditis (inflammation of the lining of the heart), pericardial effusion [a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself.
- change in colour of the tongue.

The following side effects have been reported with **children and adolescents taking ribavirin and an interferon alfa-2b product**:
Very commonly reported side effects:
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness) decrease in neutrophils (that make you more susceptible to different infections),
- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms),
- feeling depressed or irritable, feeling sick to stomach, feeling unwell, mood swings, tired feeling, trouble falling asleep or staying asleep, virus infection, weakness,
- diarrhoea, dizziness, fever, flu-like symptoms, headache, loss of or increase in appetite, loss of weight, decrease in the rate of growth (height and weight), pain on right side of ribs,

pharyngitis (sore throat), shaking chills, stomach pain, vomiting,
- dry skin, hair loss, irritation, pain or redness at the site of injection, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Commonly reported side effects:
- decrease in blood clotting cells called platelets (that may result in easy bruising and spontaneous bleeding),
- excess of triglycerides in the blood, excess of uric acid (as in gout) in the blood, increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors),
- agitation, anger, aggressive behaviour, behaviour disorder, difficulty concentrating, emotional instability, fainting, feeling anxious or nervous, feeling cold, feeling confused, feeling of restlessness, feeling sleepy, lack of interest or attention, mood changes, pain, poor quality sleep, sleepwalking, suicide attempt, trouble sleeping, unusual dreams, wanting to harm yourself,
- bacterial infections, common cold, fungal infections, abnormal vision, dry or teary eyes, ear infection, eye irritation or pain or infection, change in taste, changes in your voice, cold sores, coughing, inflamed gums, nose bleed, nose irritation, oral pain, pharyngitis (sore throat), rapid breathing, respiratory infections, scaling lips and clefts in the corners of the mouth, shortness of breath, sinusitis, sneezing, sores in mouth, sore tongue, stuffy or runny nose, throat pain, toothache, tooth abscess, tooth disorder, vertigo (spinning feeling), weakness
- chest pain, flushing, palpitations (pounding heart beat), rapid heart rate,
- abnormal liver function,
- acid reflux, back pain, bedwetting, constipation, gastroesophageal or rectal disorder, incontinence, increased appetite, inflammation of the membrane of the stomach and intestine, stomach upset, loose stools,
- urination disorders, urinary tract infection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual periods, disorder of vagina, inflammation of the vagina, testis pain, development of male body traits,
- acne, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), increased or decreased sensitivity to touch, increased sweating, increase in muscle movement, tense muscle, irritation or itching at the site of injection, limb pain, nail disorder, numbness or tingling feeling, pale skin, rash with raised spotted lesions, shaky hands, redness of skin or skin disorder, skin discolouration, skin sensitive to sunlight, skin wound, swelling due to a build-up of excess water, ,swollen glands (swollen lymph nodes), tremor, tumour (unspecified).

Uncommonly reported side effects
- abnormal behaviour, emotional disorder, fear, nightmare,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, blurred vision, drowsiness, intolerance to light, itchy eyes, facial pain, inflamed gums,
- chest discomfort, difficult breathing, lung infection, nasal discomfort, pneumonia, wheezing,
- low blood pressure,
- enlarged liver,
- painful menstruation,
- itchy anal area (pinworms or ascarids), blistering rash (shingles), decreased sensitivity to touch, muscle twitching, pain in skin, paleness, peeling of skin, redness, swelling.

The attempt to harm yourself has also been reported in adults, children, and adolescents.
Ribavirin Aurobindo in combination with an alpha interferon product may also cause:
- aplastic anaemia, pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells); this causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy,
- delusions
- upper and lower respiratory tract infection,

− inflammation of the pancreas,
− severe rashes which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes (erythema multiforme, Stevens Johnson syndrome), toxic epidermal necrolysis (blistering and peeling of the top layer of skin),

The following other side effects have also been reported with the combination of ribavirin and an alpha interferon product:
− abnormal thoughts, hearing or seeing images that are not present, altered mental status, disorientation,
− angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), stroke (cerebrovascular events)
− Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord)
− bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction), constant cough,
− eye problems including damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye and cotton wool spots (white deposits on the retina),
− enlarged abdominal area, heartburn, trouble having bowel movement or painful bowel movement,
− acute hypersensitivity reactions including urticaria (hives), bruises, intense pain in a limb, leg or thigh pain, loss of range of motion, stiffness, sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands)

Ribavirin Aurobindo in combination with peginterferon alfa-2b or interferon alfa-2b may also cause:
− dark, cloudy or abnormally coloured urine.
− difficulty breathing, changes in the way your heart beats, chest pain, pain down left arm, jaw pain,
− loss of consciousness,
− loss of use, drooping or loss of power of facial muscles, loss of feeling sensation,
− loss of vision,

You or your caregiver should call your doctor immediately if you have any of these symptoms.
If you are a HCV/HIV co-infected adult patients receiving anti-HIV treatment, the addition of Ribavirin Aurobindo in and peginterferon alfa- 2b may increase your risk of worsening liver function highly active anti-retroviral therapy (HAART) and increase your risk of lactic acidosis, liver failure and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets) (NRTI).

In HCV/HIV co-infected patients receiving HAART, the following other side effects have occurred with the combination of ribavirin hard capsules and peginterferon alfa-2b (not listed above in adults side effects):
- appetite decreased ,
- back pain,
- CD4 lympocytes decreased,
- Defective metabolism of fat,
- Hepatitis,
- Limb pain,
- Oral candidiasis (oral thrush),
- Various laboratory blood values abnormalities.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RIBAVIRIN AUROBINDO

Keep out of the reach and sight of children.
Do not use Ribavirin Aurobindo after the expiry date, which is stated on the carton/blister after EXP. The expiry date refers to the last date of that month.

This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ribavirin Aurobindo contains
- The active substance is ribavirin.

Each Ribavirin Aurobindo capsule contains 200 mg of ribavirin.

- The other ingredients are cellulose, microcrystalline, lactose monohydrate, povidone, magnesium stearate. The capsule shell contains gelatine, titanium dioxide (E171) and sodium lauryl sulphate. The capsule shell imprint contains shellac, propylene glycol, potassium hydroxide, black iron oxide (E 172).

What Ribavirin Aurobindo looks like and contents of the pack
Capsule, hard
White / White, size '1' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'E' on white cap and '81' on white body with black ink.

Ribavirin Aurobindo is available in PVC/PE/PVDC/Aluminium blisters and HDPE containers in the pack sizes of
PVC/PE/PVDC/aluminium blister: 84, 112, 140 and 168 capsules
HDPE bottle: 42 and 500 capsules

Not all pack sizes may be marketed.

Marketing Authorisation Holder
[To be completed nationally]

Manufacturer
[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany	Ribavirin Aurobindo 200 mg Hartkapseln
Spain	Ribavirina Aurobindo 200 mg cápsulas duras EFG
France	Ribavirine Aurobindo 200 mg, gélule
Italy	Ribavirina Aurobindo
Portugal	Ribavirina Aurobindo
Romania	Ribavirin Aurobindo 200 mg capsule
United Kingdom	Ribavirin 200 mg capsules

This leaflet was last approved in {MM/YYYY}
[To be completed nationally]