PHASE Ib/II STUDY OF UPROLESELAN ADDED TO CLADRIBINE PLUS LOW DOSE CYTARABINE (LDAC) INDUCTION FOLLOWED BY CONSOLIDATION WITH UPROLESELAN PLUS CLADRIBINE PLUS LDAC IN PATIENTS WITH TREATED SECONDARY AML (TS-AML)

1.0 OBJECTIVES

1. Primary objective:

- To determine the safety, tolerability, and recommended phase II dose (RP2D) of uproleselan combined with cladribine + low dose cytarabine (LDAC) in patients with treated-secondary AML (ts-AML)

2. Secondary objectives:

- To assess the efficacy (overall response rate [ORR], complete response [CR], complete response without blood count recovery [CRi], CR with partial hematologic recovery [CRh], partial response [PR], or morphologic leukemia-free state (MLFS) of uproleselan combined with cladribine + LDAC in patients with ts-AML.
- To assess the rate of minimal residual disease (MRD) negativity by flow cytometry at response.
- To assess overall survival (OS), remission duration (CRd), and progression-free survival (PFS) in patients with ts-AML treated with uproleselan combined with cladribine + LDAC.
- To assess the rate of complete cytogenetic response (CCyR) in patients with ts-AML with abnormal baseline karyotype, treated with uproleselan combined with cladribine + LDAC.
- To assess toxicity and induction mortality of patients with AML treated with uproleselan added to cladribine + LDAC.

3. Exploratory objective:

- To explore biomarkers of response and resistance in patients with ts-AML treated with uproleselan combined with cladribine + LDAC.
- To examine the correlation of E-selectin ligand-forming glycosylation genes of leukemic blasts with clinical outcome.

2.0 BACKGROUND

2.1 Acute Myeloid Leukemia (AML)

AML is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 10,000 new cases per year. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to > 10 per 100,000 in the elderly. AML represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere.[1,2] AML is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow

and in the peripheral circulation. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival in younger patients, but provides little benefit for patients who are older than 60 years. Overall, up to 70% of patients can be expected to relapse, so that only about 20-30% attain long-term disease-free survival.

A number of risk factors have been identified that predict the length of remission and the possibility of long-term survival. Age has emerged as a major factor that determines the prognosis of patients with untreated AML. For those patients, treatment has not improved significantly in recent years when compared with the progress that has been made in younger patients.[3-5] AML occurring in patients > 60 years of age thus continues to carry a poor prognosis. Using a standard induction combination such as the 3+7 regimen (cytarabine plus an anthracycline), complete remission rates decrease by about 10% per additional decade of life, induction mortality can be substantial, easily exceeding 20%, and remission durations are usually transient and rarely last more than 12 months. The median time from treatment to death is 5 to 10 months and less than 10% of patients stay in remission at 3 years.[3] We recently reviewed our own experience in older patients treated between 1990 and 2009 with intensive chemotherapy. In 446 patients, the overall CR rate was 45%, with a 4-week mortality of 26%, an 8-week mortality of 36%, a 1-year survival rate of 28%, and a median overall survival of 4.6 months. The reasons for this difference in outcome when compared to younger patients are multiple. Differences in the biology of AML in older patients is reflected by a higher proportion of patients with an unfavorable karyotype, a higher rate of primary drug resistance associated with overexpression of P-glycoprotein (P-gp), and an increased frequency of disease evolution from a preexisting and at times probably unrecognized myelodysplasia. Poorer tolerance of combination chemotherapy regimens leads to the use of less intensive treatment protocols.[6] Acknowledging the particular challenges posed by older patients with AML both based on patient and disease-related factors, considerable efforts are being invested in targeting this particular group of patients. Realizing the poor response with standard therapy, new agents and newer strategies are continuously being studied. The development of new and effective anti-AML approaches therefore remains a cornerstone of the continued efforts to improve the outcome of poor prognosis patients.[7] Both cladribine and 5-azacytidine have been studied in myeloid disorders and are the main ingredients of the proposed study.

2.12 Treated-secondary AML (ts-AML)

Secondary AML refers to a subset of AML that arises from a prior or antecedent myeloid disorder such as myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), or aplastic anemia. These are known to be clonal myeloid neoplasms with a high risk of transformation to AML as part of their natural history. Recently, the World Health Organization (WHO) has revised its

classification schema of AML to include a subset of "AML with MDS-related changes", which includes (1) AML arising from prior MDS/MPN, (2) AML with MDS related cytogenetic abnormality, and (3) AML with morphologic evidence of multilineage dysplasia. Compared to so-called 'de novo' AML, secondary AML has been associated with a poor overall prognosis, with lower response rates to standard therapy and an overall inferior survival outcome.

With the introduction of hypomethylating agents (HMAs) such as 5-azacytidine (AZA) and decitabine, treatment of antecedent hematologic disorders such as MDS and MPN has improved, with improved OS and reduced transformation to AML. However, the increased use of HMAs has led to a growing cohort of patients with AML who have had an antecedent myeloid malignancy (MDS or MPN) and have been treated for that malignancy with HMAs. These patients, classified as having treated-secondary AML (ts-AML) have recently been shown to have a particularly adverse prognosis and should likely be considered a separate high-risk cohort that needs effective new approaches.

We recently reviewed our experience of ts-AML treated over 15 years to define their overall prognosis and response to differential therapeutic approaches (Boddu P, et al 2017). A total of 254 patients with ts-AML were examined and compared to patients without ts-AML, including those with s-AML and de novo AML. Overall, patients with ts-AML had a median OS of 4.2 months compared to 9.2 months in patients with untreated s-AML ($P < 0.001$). This poor survival was evident in patients < 60 years of age (median OS, 5 months) and those $\geq$ 60 years of age (median OS, 4.7months). Emphasizing its particularly adverse prognosis, patients with ts-AML had median OS that was inferior to other well established high-risk subgroups, including those with TP53 mutations, monosomy 5/7, chromosome 3q abnormalities, and those with therapy related AML.

We also reviewed response rates and mortality rates by treatment intensity, divided into high intensity ($\geq$ 1 gram/m2 of cytarabine), moderate intensity (100 – 500 mg/m2 of cytarabine), or lower intensity (low dose cytarabine combinations or HMAs). High intensity therapy produced CR/CRp rates of 26% and 32% among younger and older patients respectively, but were associated with 8-week mortality rates of 35% and 32%, respectively. Moderate intensity approaches yielded CR/CRp rates of 43% and 27%, respectively, along with 8-week mortality rates of 14% and 36%, respectively. When using lower intensity therapies, CR/CRp rates were 11% and 22%, respectively among younger and older patients, with associated 8-week mortality rates of 22% and 19%, respectively.

These adverse outcomes across different therapy intensities, and without regard to age, highlights an important area of unmet need that requires focused research on newer therapies. We have designed the current study to investigate a combination that may help improve outcomes in this difficult subset of patients.

2.2 Cladribine in AML

Cladribine (2-chloro-2'-deoxyadenosine, 2-CDA) is a synthetic purine nucleoside analogue that is currently FDA approved for the treatment of symptomatic Hairy Cell leukemia.[8] Based on the success of cytarabine (AraC) in leukemia, 2-CDA was rationally designed to be resistant to degradation by adenosine deaminase and thereby increase its cytotoxicity. Cladribine's cytotoxic effects have been attributed to its ability to interfere with DNA synthesis in replicating cells[9] as well as inhibition of DNA repair and accumulation of DNA strand breaks in nonproliferating cells[10,11]. Clinically, 2-CDA has been shown to have single-agent activity in hairy cell leukemia, chronic lymphocytic leukemia, as well as acute myeloid leukemia.[12,13] Building on a phase I study in pediatrics[14] that confirmed safety and potential efficacy, Santana et. al.[15] conducted a phase II study of 2-CDA in pediatric patients with relapsed AML and ALL. Patients were given 2-CDA as a 5-day continuous infusion at a dose of 8.9 mg/m^2/d. Of 17 patients with AML, 8 (47%) achieved a CR and 2 (12%) achieved a PR, for an overall response rate of 59%. The drug was very well tolerated with the major toxicity being severe myelosuppression.

These initial promising results in pediatric AML led to follow-up studies in adults. In a phase I study of adults with relapsed or refractory AML, patients were given 2-CDA at doses ranging from 5 to 13 mg/m^2/d by continuous infusion for 7 days.[16] Of the 27 patients treated, 2 died before they could be evaluated and 16/25 remaining patients cleared their bone marrow of leukemia with regrowth in 9 patients after a median of 2 weeks. There were no complete remissions in this population. Toxicity was mild except for 3 cases of grade III or IV renal dysfunction. The MTD was defined as 10.8 mg/m^2/d x 7 days. The authors concluded that 2-CDA was a potent cytoreductive agent in adult AML, but not sufficient as a single-agent to yield CRs in this relapsed population. The importance of this study is that it served as a lead-in to a combination trial with AraC[16,17] that utilized intracellular pharmacodynamic data and was based on preclinical models of synergy between the 2 compounds.[18]

The cytotoxicity and clinical activity of AraC, the most active agent in AML, is directly related to the intracellular generation and retention of ara-CTP (the triphosphate form). Strategies that increase intracellular ara-CTP are therefore desired to increase its activity. 2-CDA is a potent inhibitor of ribonucleotide reductase and therefore leads to a significant decrease in intracellular deoxynucleotide pools. This has 2 major effects with respect to intracellular AraC. First, it augments the activity of deoxycytidine kinase which rapidly generates intracellular ara-CTP from AraC. Second, as a result of the depletion of normal intracellular deoxynucleotides, ara-CTP and Cd-ATP (the triphosphate form of 2-CDA) become more prominent as substrates for DNA polymerase in dividing cells. They are more likely to get incorporated into DNA and exert their cytotoxic effects. This hypothesis has been confirmed in preclinical studies. In vitro incubation of AML blasts with 2-CDA followed by AraC produced a higher rate of ara-CTP accumulation than AraC alone.[19]

As an extension of the aforementioned phase I study of 2-CDA in adults with AML, a phase II study combining AraC 1 g/m^2 with 2-CDA 12mg/m^2/d x 5 days was conducted to test this hypothesis clinically.[16,17] Of the 17 patients treated, 2 patients achieved a CR (12%) and 69% cleared their bone marrow. Correlative studies from this trial confirmed a median 40% increase in the rate of ara-CTP accumulation in the leukemia blasts of patients after pretreatment with 2-CDA. In addition, the DNA synthetic capacity of the circulating blasts was inhibited to a greater extent by administration of 2-CDA and AraC in combination than by either one alone. Both 2-CDA and AraC (CdAMP and ara-CMP, respectively) were found to be incorporated into DNA, with the tandem incorporation having the most potent chain-termination effect.[17] This strategy of combining a potent ribonucleotide reductase inhibitor with AraC to increase its clinical activity has been successfully replicated using other nucleoside analogues such as fludarabine[20-22] and clofarabine.[23]

Based on this data, several groups have studied combinations of 2-CDA and different doses of AraC in the treatment of AML. In a multicenter phase II study[24] from the Polish Adult Leukemia Group (PALG) 58 patients with refractory AML (50 primarily resistant and 8 with short CR durations) were treated with 2-CDA (5 mg/m^2/d IV over 2 hrs x 5 days) combined with AraC (2 g/m^2/d IV over 4 hrs - starting 2 hrs after CDA x 5 days) and G-CSF (300 µg subcutaneously daily x 6 days). The CR rate was 50%. Notably 5/6 (83%) of patients with MDS/AML achieved a remission. Myelosuppression was the most prominent toxicity. The 1-yr overall survival for the entire cohort and for those who achieved a CR was 42% and 65%, respectively and the disease free survival (DFS) at 1 year was 29%.

Investigators from Sweden conducted a randomized phase II trial[25] in de novo AML patients aged > 60 years, comparing the combination of 2-CDA + AraC + idarubicin (CCI) to AraC + idarubicin (CI). A total of 63 patients with a median age of 70 years were randomized 2:1 to treatment with 2-CDA (5 mg/m^2/d IV over 1 hr x 4 days) plus ara-C (1 g/m^2/d IV over 2 hrs x 4 days) plus idarubicin (10 mg/m^2/d IV over 1 hr x 2 days) versus the 2 drug combination. The CR rate was 51% for CCI vs 35% for CI (p=0.014). There were no differences in toxicity between the 2 arms. The median overall survival was 14 months, with a 2-year survival over 30%. There was no significant difference in survival between the 2 arms.

The PALG conducted a similar study combining 2-CDA, an anthracycline, and a lower dose of AraC in younger patients with untreated AML. Among 50 patients treated with 2-CDA (5 mg/m^2/d IV over 1 hr x 5 days) plus ara-C (200 mg/m^2/d IV x 7 days) plus daunorubicin (60 mg/m^2/d IV daily x 3 days), the CR rate was 72%. This led to the phase III multicenter study[26] comparing this combination (DAC-7) with daunorubicin and ara-C without cladribine. A total of 400 patients with a median age of 45 were randomized to the daunorubicin plus cytarabine (DA-7) or the 3-drug combination outlined above (DAC-7). The CR rate after a single course of therapy was 64% for DAC-7 vs. 47% for DA-7 (p=0.0009). The

median hospitalization time was shorter for DAC-7 vs. DA-7 (33 vs. 40 day, p=0.002). Toxicity was comparable between both groups and primarily consisted of myelosuppression and its sequelae. Overall, the probability of leukemia free survival (LFS) was 43% and 34% between DAC-7 and DA-7, respectively (p=NS). However, in patients aged > 40 years, there was a trend for higher LFS in those who received DAC-7 (44% vs. 28%, p=0.05). These studies demonstrate tolerability and suggest enhanced antileukemia efficacy with the addition of cladribine to induction regimens, particularly in older patients and those with MDS/AML.

2.3 Cladribine + Low Dose AraC (LDAC) in AML

Based on the observation of synergy and clinical efficacy of the combination of cladribine and cytarabine as part of an intensive regimen in AML, we designed a lower intensity approach combining cladribine with lower doses of cytarabine for older and unfit patients with newly diagnosed AML. The regimen combines cladribine 5 mg/m2 IV on D1-5 with low dose cytarabine (LDAC) at a dose of 20mg SQ twice daily on D1-10 of a 28 day cycle. The goal was to produce higher rates of response while maintaining excellent tolerability. We recently published our experience with the cladribine/LDAC regimen with a median follow-up of 30+ months, achieving these goals (Kadia 2018).

The report included 118 patients with a median age of 69 years (range, 49-85) with 41% having an adverse karyotype. The overall response rate was 68%, including a CR rate (with complete count recovery) of 58% and a CRi rate of 9%. The CR duration was 14.7 months and the median overall survival was 13.8 months overall, one of the longest reported historically among older patients with AML. Among patients with a diploid karyotype, the median OS was 19.9 months.

When we reviewed outcomes of patients with ts-AML treated with a cladribine/LDAC based regimen, we observed a CR rate of 39%, and CRp rate of 8% for a CR/CRp rate of 47% (Boddu 2017). The therapy was associated with a 4-week mortality of 3% in this difficult population. Based on our own historical experience with older AML and from published data, this backbone of Cladribine/LDAC alternating with HMA represented a significant improvement from the standard HMA-based lower intensity therapy in AML. It represents a safe and effective backbone of chemotherapy that we can build on to continue and improve results.

2.4 Clinical Experience with Uproleselan in AML

Binding of E-selectin within the microenvironment, to the leukemic cell surface, activates cell survival pathways and promotes chemotherapy resistance in AML. Expression of the E-selectin ligand is associated with increased risk of relapse and poor survival in AML. Uproleselan is a novel E-selectin antagonist that disrupts cell survival pathway activation, enhances chemotherapy response, and

protects from toxicity with improved survival in *in vivo* models. Uproleselan has been studied in combination with chemotherapy in patients with treatment naïve (TN) and R/R AML.

Ninety-one patients, including 25 with TN AML were enrolled on a phase I/II trial to assess safety and efficacy of uproleselan combined with chemotherapy. Patients with R/R AML were treated with uproleselan combined with mitoxantrone, etoposide, and cytarabine (MEC). Dose escalation established the recommended phase II dose (RP2D) uproleselan with chemotherapy to be 10 mg/kg. Among 66 patients with R/R AML with a median age of 59 years, the CR/CRi rate was 39% and 41% at the RP2D; 69% of patients evaluable for MRD were negative at the time of response. The median OS in this population was 8.8 months at the RP2D. Among patients treated with this uproleselan combination, intensity of the E-selectin ligand expression correlated with MRD negative response and the higher E-selectin ligand expression on leukemic stem cells (LSC) correlated positively with responders and overall survival.

Patient with TN AML were treated with uproleselan combine with 7+3. The median age of these 25 patients was 67 years (range, 60-79), with 48% having adverse karyotype and 52% with secondary AML. The combination was well tolerated with a CR/CR rate of 72% overall and 69% among patients with secondary AML. The median OS was 12.6 months. The median LSC expression of E-selectin ligand among responders and non-responder was similar in this untreated population. Phase III studies in patients with R/R AML and older AML are underway.

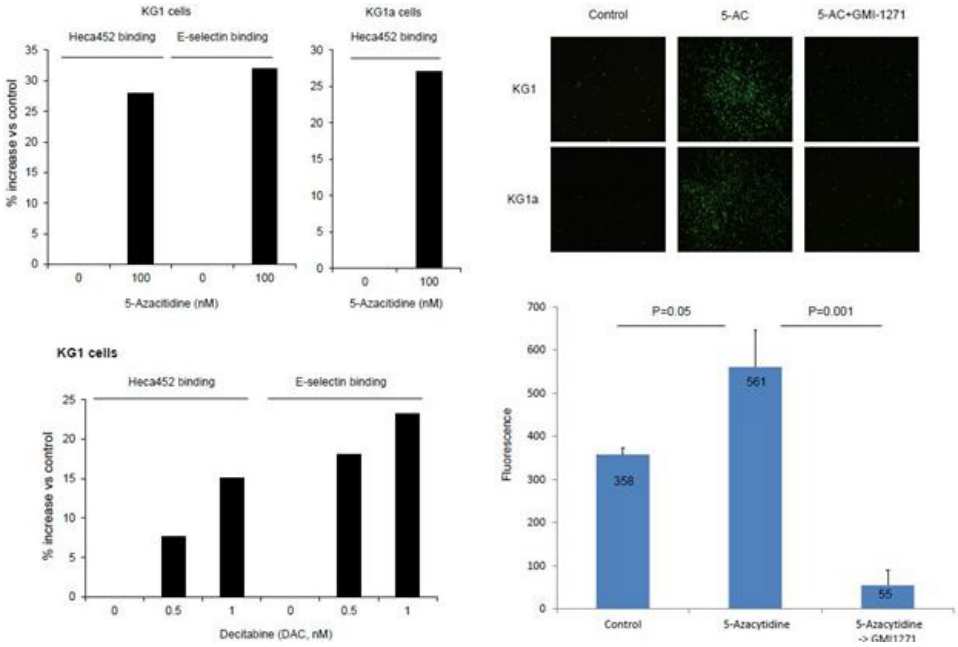
2.4.2 Rationale for studying cladribine, ara-C, and Uproleselan in patients with ts-AML

Treated secondary AML (ts-AML) or patients often referred to as having "hypomethylating agent (HMA) failure" is a group defined as having had HMA treatment for a prior myeloid neoplasm prior to developing AML (≥ 20% blasts). These are most often patients with myelodysplastic syndrome (but also with myeloproliferative neoplasms) treated for months or years before transforming into AML. With the widespread and growing use of HMA for these patients, and in the context of an aging population with higher incidence of MDS, this is a subset of patients that is steadily growing.
As we and others have shown, the prognosis of patients with ts-AML is extremely poor, representing among the worse outcomes across AML subtypes – with a median OS of approximately 4.7 months (regardless of age), low response rates to chemotherapy, and high rates of early mortality. In this setting, there are very limited options. Using another HMA in a setting where the disease has just progressed on HMA therapy is not desirable nor effective. New therapies with good safety profile and high efficacy are needed.

In the early clinical studies of uproleselan in AML, E-selectin ligand expression and functional binding with uproleselan was significantly associated with

achieving CR/CRi among previously treated patients. Furthermore, higher E-selectin ligand expression among patients treated with uproleselan was associated with higher rates of MRD negativity and superior OS.

Preclinical studies have demonstrated that exposure of AML cells to HMAs actually increases expression of E-selectin ligand on blasts, an effect that is quenched by the addition of uproleselan (Figure). Among patients with ts-AML, who have presumably had prolonged prior exposure to HMA therapy, E-selectin expression is likely upregulated, serves as a mechanism of chemoresistance, and provides a rational target for combination therapy with uproleselan.



We therefore propose the current study, combining the E-selectin antagonist uproleselan with an active, lower-intensity chemotherapy backbone, for patients with ts-AML.

2.5 Cladribine

Cladribine is available commercially.

Cladribine Injection (also commonly known as 2-chloro-2′-deoxy-ß-D-adenosine) is a synthetic antineoplastic agent for intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. Cladribine Injection is available in single-use vials containing 10 mg (1 mg/mL) of Cladribine, a chlorinated purine nucleoside analog. Each mL of Cladribine injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3 ± 0.3.

The selective toxicity of 2-chloro-2′-deoxy-ß-D-adenosine towards certain normal and malignant leukocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2′-deoxy-ß-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2′-deoxy-ß-D-adenosine is resistant to deamination by adenosine deaminase, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2′-deoxy-ß-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2′-deoxy-ß-D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2′-deoxy-ß-D-adenosine is cytotoxic to both actively dividing and quiescent cells, inhibiting both DNA synthesis and repair.

Cladribine plasma concentration after intravenous administration declines multi-exponentially with an average half-life of 6.7 + 2.5 hours. In general, the apparent volume of distribution of Cladribine is approximately 9 L/kg, indicating an extensive distribution in body tissues.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

Cladribine is bound approximately 20% to plasma proteins.

2.6 Cytarabine

Cytarabine is available commercially.

Cytarabine is a deoxycytidine analog that is metabolized to cytarabine triphosphate, a substance that inhibits DNA polymerase. It is S phase specific, and thus affects DNA synthesis. It has an initial plasma half-life of about 15 minutes, with a secondary phase of about 2 hours, and is rapidly catabolized by hepatic cytidine deaminases to Ara-U.

Cytarabine injection, an antineoplastic is a sterile solution of cytarabine for intravenousadministration. Each mL contains 20 mg cytarabine in 100 mg (20 mg/mL) single dose vials and 100 mg cytarabine in 2 g (100 mg/mL) single dose vial.

Cytarabine injection 100 mg/5 mL is a sterile solution for intravenous administration. Each mL contains 20 mg cytarabine USP, and the following inactive ingredients: sodium chloride 6.8 mg and Water for Injections qs. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.7.

Chemical stability studies were performed by ultraviolet assay on cytarabine injection in infusion solutions. These studies showed that when cytarabine injection was added to Water for Injection, 5% Dextrose in Water or Sodium Chloride Injection, 94% to 96% of the cytarabine was present after 192 hours storage at room temperature. Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

2.7 Uproleselan injection, 50 mg/mL

The investigational product, uproleselan injection, 50 mg/mL, is a sterile, isotonic solution for IV administration. The drug substance is present as the sodium salt; however, the solution concentration is based on the free-acid active moiety. The formulation contains precedented compendial excipients. The sodium content of the formulation is 3.3 mg/mL. The clinical product formulation includes 10 mM Tris buffer to stabilize the pH at 7.4 (6.4 to 8.4).

Uproleselan injection is supplied in single-dose vials at a concentration of 50 mg/mL. Uproleselan injection 50 mg/mL is stored per the specified conditions on the label, either frozen (10 °C to -25 °C) or refrigerated (2-8°C), prior to administration. The frozen product can appear as a homogenous solid, a striated solid, or as a super-cooled liquid. When using frozen supply, vials should be brought to room temperature before dose preparation. Upon thawing, the product should be gently inverted 4 to 5 times to ensure homogeneity of the solution. The thawed solution is clear, colorless to slightly yellow, and free from visible particulates. Reconstitution and dilution are not necessary. Dilution up to 10X may be performed with normal saline.

Uproleselan injection should be administered IV into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC).

Infusion should take place at a steady rate over a period of 20 minutes using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration is highly recommended.

Compatibility with other therapeutic agents has not been determined; therefore, uproleselan injection should be administered via a separate IV line and should not be administered concurrently with anything other than saline. If a flush is used, saline flush is preferred.

When prepared in syringes or intravenous (IV) bags without an administration set attached, uproleselan may be stored refrigerated up to 72 hours prior to administration or up to 24 hours at controlled room temperature prior to administration. Administration sets manufactured from materials of construction other than polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP) can be primed up to 72 hours before dosing if stored refrigerated or up to 24 hours before dosing if stored at controlled room temperature. Intravenous lines consisting of PVC with DEHP should be avoided when possible. If PVC with DEHP administration sets must be used they should be primed with uproleselan solution no more than 2 hours before dosing. It is highly recommended that uproleselan prepared prior to administration be refrigerated until 1 hour prior to dosing.

Uproleselan is to be kept in a locked and secured storage facility, accessible only to those individuals authorized by the principal investigator (PI).

3.0 PATIENT SELECTION

3.1 Inclusion Criteria:

1. Patients with a diagnosis of treated secondary-AML (TS-AML) who have not received therapy for their AML will be eligible.
2. TS-AML is defined as AML arising from a previously treated antecedent myeloid neoplasm (myelodysplastic syndrome or myeloproliferative neoplasm that has been previously treated with hypomethylating agents).
3. Patients must be at least 7 days from their last therapy for the antecedent myeloid neoplasm
4. Age >/= 18 years.
5. Adequate organ function as defined below:
   - liver function (total bilirubin ≤ 2mg/dL, AST and/or ALT ≤3 x ULN – or ≤5 x ULN if related to leukemic involvement)
   - kidney function (creatinine ≤ 1.5 x ULN).
   - known cardiac ejection fraction of > or = 45% within the past 6 months
6. ECOG performance status of ≤ 2.
7. A negative urine or serum pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial.
8. Patient must have the ability to understand the requirements of the study and informed consent. A signed informed consent by the patient is required prior to their enrollment on the protocol.

3.2 Exclusion Criteria

1. Pregnant women are excluded from this study because the agents used in this study have the potential for teratogenic or abortifacient effects. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with the chemotherapy agents, breastfeeding should also be avoided.

2. Uncontrolled intercurrent illness including, but not limited to active uncontrolled infection, symptomatic congestive heart failure (NYHA Class III or IV), unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
3. Patients with documented hypersensitivity to any of the components of the chemotherapy program.
4. Men and women of childbearing potential who do not practice contraception. Women of childbearing potential and men must agree to use contraception prior to study entry and for the duration of study participation.
5. Prior treatment with uproleselan.
6. Patients with a diagnosis of acute promyelocytic leukemia (AML-M3) will be excluded from this study.

4.0 TREATMENT PLAN

This is a single arm phase Ib/II study in which patients will be treated with uproleselan given intravenously, combined with cladribine, (2-CDA, given intravenously [IV]) in combination low dose cytarabine (LDAC, given subcutaneously [SQ]) as induction therapy, followed by up to 6 cycles of consolidation/maintenance therapy composed of 2-CDA + LDAC (according to schema below) also in combination with uproleselan. In patients who do not achieve CR/CRi/MLFS after cycle 1, an additional course of re-induction with 2-CDA+LDAC+uproleselan may be given.

Treatment will be continued during the duration of the study unless patient exhibits evidence of clinically significant treatment failure, clinically significant disease progression, unacceptable toxicity, or if the investigator determines that discontinuation is in the best interest of the patient. Patients who do not achieve at least MLFS after two cycles of therapy will be taken off study. Relapsing patients may remain on the study if participation in the study is still providing disease control or clinical benefit and is considered in the best interest of the patient after discussion with the principal investigator.

Patients will be treated with the study drugs per protocol, based on the calculation of the patient's body surface area (BSA). The BSA will be calculated before each cycle and will be based on the patient's height and weight.

Patients will be instructed to self-administer cytarabine at home unless hospitalized and return unused drug in accordance with institutional guidelines. All induction and consolidation intravenous infusions will be administered at MD Anderson Cancer Center (MDACC) or at the MDACC Houston Area Locations (HALs).

The primary objective is to determine the safety of this combination and also to determine efficacy in achieving CR, CRi; and prolonging RFS and OS. All patients will be registered for the protocol via the Clinical Oncology Research (CORe) system at MDACC (single institution study).

The study will have 2 dose levels during lead-in, followed by an expansion cohort of 25 patients at the safe and tolerable dose level. All patients will be treated with the RP2D of uproleselan of 800 mg IV on D1 and then IV q12 hours on D2-12.

During safety lead-in, we will use the BOIN design (see section 8.0) to identify the RP2D of the combination therapy. During phase II, 25 additional patients will be enrolled at the RP2D level to confirm safety and to assess preliminary efficacy.

4.1 Treatment Schema (4-week cycles +/- 7 days)

4.1.1 Induction therapy will consist of:

A. Uproleselan 800 mg IV on D1 and then 800mg IV Q12 hours (+/- 2 hours) on D2-12 approximately 1 hour prior to cladribine (+/- 15 minutes).

B. Cladribine at the assigned dose level IV over approximately 1 to 2 hours, daily on days 1-5 combined with cytarabine at the assigned dose level SQ twice daily on days 1-10. The cytarabine should be administered approximately 3-6 hours following the start of the cladribine infusion.

4.1.1.1 Patients who do not achieve a CR or CRi after cycle 1 may proceed with a second induction cycle as noted in Table 2 below.
4.1.1.2 Patients who do not achieve a CR or CRi after cycle 2 may continue on protocol (as shown in Table 2) as long as the patient is deriving clinical benefit in the opinion of the investigator.

4.1.2 Consolidation/Maintenance therapy will consist of:

(A) Uproleselan 800 mg IV on D1 and then 800mg IV Q12 hours (+/- 2 hours) on D2-12 approximately 1 hour prior to cladribine (+/- 15 minutes). In patients who have achieved at least CR/CRi or morphologic leukemia-free state, uproleselan will be given ONCE daily on D1-12.

(B) Cladribine at the assigned dose level IV over 1 to 2 hours, daily on days 1-3 combined with Cytarabine at the assigned dose level SQ twice daily on days 1-10. The cytarabine should be administered 3-6 hours following the start of the cladribine infusion.

Table 1.	**Dose Escalation Table**	
Dose level	Cladribine (mg/m^2 IV daily on days 1-5)*	Cytarabine (mg SQ twice daily on days 1-10)
1	5	20
-1	3.75	15

One cycle of therapy is considered 4 weeks. Subsequent cycles may be started within 4-7 weeks after the start of the previous cycle depending on hematopoietic recovery and resolution of toxicities in the judgment of the

treating physician. Subsequent cycle delay beyond 7 weeks may be allowed after discussion with the principal investigator and documentation of the discussion.

Patients with progressive or proliferating disease requiring initiation of a subsequent cycle of chemotherapy prior to day 28 of a previous cycle may start therapy no earlier than day 21 of a previous cycle after discussion with the principal investigator and documentation of the discussion.

The flow of treatment schema is outlined in the table below:

Table 2.

Cycle Number	Induction	Consolidation
1	Cladribine IV daily on days 1-5 Cytarabine SQ twice daily on days 1-10 Uproleselan 800 mg IV on D1 and then 800mg IV Q12 hours on D2-12	**NOT APPLICABLE**
2	**<IF RE-INDUCTION IS INDICATED>** Cladribine IV daily on days 1-5 Cytarabine SQ twice daily on days 1-10 Uproleselan 800 mg IV on D1 and then 800mg IV Q12 hours on D2-12	**<IF PT ACHIEVES CR or CRi or MLFS after CYCLE 1>** Cladribine IV daily on days 1-3 Cytarabine SQ twice daily on days 1-10 Uproleselan 800 mg IV daily on D1-12
3 - 6		Cladribine IV daily on days 1-3 Cytarabine SQ twice daily on days 1-10 Uproleselan 800 mg IV daily on D1-12

4.1.3 Definition of DLT

Dose Limiting Toxicity (DLT) - DLT will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5) by organ system. DLT will be defined as adverse events during cycle one.

A) Grade 3 or greater, non-hematologic toxicities at least possibly related to study treatment will be considered DLTs.Any Grade 3 nausea, vomiting or diarrhea that requires hospitalization, tube feeding or TPN is a DLT unless definitely attributed to a different cause. As the following are common events in patients with leukemia (> 50%), they will not be used for the definition of DLT: prolonged myelosuppression (grade 3 - 4), neutropenic fever without infection (grade 3), non-neutropenic fever (grade 3), infections with grade 3 and 4 neutropenia [exception – see bullet E below], infections without neutropenia (grade 3) [exception – see bullet E below], readmission associated with NCI grade 3 toxicity, cytopenias not

resulting in death, transfusions of platelets and packed RBCs (grade 3), low blood pressure due to dehydration requiring fluid replacement, abnormalities of LDH (lactate dehydrogenase) and alkaline phosphatase, tumor lysis syndrome related to disease bulk (grade 3-4), disturbances in electrolytes (magnesium, phosphorus, calcium), alopecia, nausea and vomiting (if manageable with supportive care measures). Grade >/= 4 non-hematologic organ toxicities that are not definitely attributed to another reason will be considered DLTs.

B) Grade 4 neutropenia or thrombocytopenia lasting beyond day 42 of the cycle in the absence of leukemia. Anemia will not be considered a hematologic DLT.

C) Any adverse reaction that leads to dose reduction or withdrawal should be considered a DLT. For the following, if not definitively related to disease or concomitant drugs: Grade 3 transaminitis (AST/ALT) elevation that does not return to Grade 1 or lower within 72 hours is a DLT. Grade 3 electrolyte abnormalities (Na, K, Cl, CO2, Ca, Mg, phosphate) that do not return to Grade 1 or lower within 72 hours is a DLT.

D) Any grade 3 liver abnormality conforming to Hy's Law will be considered a DLT unless it resolves within 72 hrs. The criteria for Hy's Law are as follows: (1) 3-fold or greater elevations above the ULN of ALT or AST; (2) concomitant elevation of serum total bilirubin to >2x ULN, without findings of cholestasis (or elevated serum ALP), and (3) No other reason can be found to explain the combination of increased transaminases and bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

E) Any grade 3 infection lasting for more than 7 days without improvement when leukemia is in remission is considered a DLT. Any grade 3 bleeding with thrombocytopenia worsening and uncontrolled by appropriate measures when leukemia is in remission is considered a DLT.

4.2 Supportive Care Measures during treatment

Necessary supportive measures for optimal medical care can be given throughout the study as indicated by the treating physician's assessment of the patient's medical need and by the institutional guidelines. Administration of antiemetics during drug administration and throughout treatment course is permitted as clinically indicated and according to departmental guidelines. Blood products should be transfused as indicated and in accordance with institutional guidelines. The use of other anti-leukemia therapy is not allowed during the course of therapy except for hydroxyurea which is allowed for the first 3 cycles of therapy only. Concomitant intrathecal chemotherapy and/or radiation therapy is permitted where indicated in patients with extramedullary disease.

4.2.1 Hematopoietic growth factors

Hematopoietic growth factors such as filgrastim or pegfligrastim (GCSF) is permitted as clinically indicated at the discretion of the treating physician.

4.2.2 Infection prophylaxis

Antibacterial, antifungal, and antiviral agents may be used in patients being treated on this study in accordance with the standard of care.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, the treatment will be administered approximately once every 4 weeks for up to 6 cycles. The patient will continue on the study unless one of the following criteria applies:

- Clinically significant progressive disease as defined by Modified International Working Group Criteria **(see section 9)** without evidence of clinical benefit**.** (Patients who have not had at least 50% reduction in bone marrow blasts by 4-6 cycles would be considered not to have clinical benefit and will come off study).
- Possibility of undergoing allogeneic bone marrow transplant.
- Intercurrent illness that prevents further administration of treatment.
- Patient request.
- Unacceptable toxicity.
- Need for further, alternative treatment.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating physician.

5.0 PATIENT EVALUATION

AML patients are typically admitted for the first month of therapy in the hospital and monitored daily for toxicities by oncologists. Following the first cycle, they are seen frequently by mid-level providers or oncologists throughout their treatment course. Toxicities are assessed by history, physical, and review of laboratory and radiologic data. These are reported to the research nurse coordinator, treating MD, and/or PI, given attribution and documented in the EMR on study interim notes. Toxicity logs will be utilized to record adverse events.

5.1 Pretreatment Evaluation. (To be completed within 14 days of study entry unless otherwise indicated)

a. History and physical examination, including vital signs, height, weight and performance status.

b. Bone marrow aspirate and/or biopsy (Cytogenetics, flow cytometry and molecular studies performed as appropriate) within 7 +/- 3 days of treatment start.
c. Biomarker testing for correlative studies will be collected as described in section 5.4.
d. CBC with differential (within 3 days) (differential not required if WBC ≤0.5 $x10^9$/L).
e. Serum chemistry: BUN, creatinine, bilirubin, AST and/or ALT, Magnesium, glucose, uric acid, (within 3 days).
f. Serum coagulation studies: PT/PTT/INR; (within 3 days)
g. Urine or serum pregnancy test within one week for women of childbearing potential.
h. Signed informed consent.

5.1 During Treatment Evaluation (Cycle 1)

a. Physical examination (including vital signs) 3 times per week.
b. CBC with differential (differential not required if WBC ≤0.5 $x10^9$/L), 3 times per week (or as clinically indicated) until remission, then every 2 to 4 weeks during active treatment, and then every 4 to 8 weeks thereafter as long as they are on study.
c. Serum chemistry profile (including uric acid) 3 times per week for the first 4 weeks and then every 2 to 4 weeks during active treatment.
d. Biomarker testing for correlative studies on D1, 5, 10, and 12 of cycle 1 as summarized in section 5.4.
e. Evaluation of toxicity assessment prior to each cycle.

5.2 During Treatment Evaluation (Cycle 2 and beyond).

a. Physical examination (including vital signs, weight, performance status) prior to each cycle.
b. CBC with differential (differential not required if WBC ≤0.5 $x10^9$/L), at least 1-2 times per week (or as clinically indicated) until remission, then every 2 to 4 weeks during active treatment, and then every 4 to 8 weeks thereafter as long as they are on study.
c. Serum chemistry profile at least once weekly until remission and then every 2 to 4 weeks during active treatment.
d. Evaluation of toxicity assessment prior to each cycle.

5.3 Outcome assessments

a. Bone marrow aspiration and/or biopsy starting on day 21 (+/- 7 days) of therapy and then every 2 weeks (+/- 7 days) as required by leukemia evolution until remission or non-response. Bone marrow tests may be ordered more frequently as indicated by changes in peripheral blood counts. No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a

WBC <0.4 x10^9/L, if the bone marrow is considered non-contributory by the investigator at any point.

b. Patients will be followed for relapse and survival every 6 to 12 months after completion of active treatment and while still on study or be enrolled on the leukemia department long-term follow-up umbrella protocol. This may be completed by phone call if the patient is not coming for routine visits.

5.4 Correlative Studies

The presence of the E-selectin ligand on AML blasts in the bone marrow will be assessed using flow cytometry. Gene expression profiling via RNA analysis will be performed to include the quantification of gene products responsible for E-selectin ligand expression. Levels of soluble E-selectin will be assessed using ELISA. Samples will be obtained as detailed in the Correlative Study Collection Table and sent to a central laboratory for testing. Any missed collection of samples for correlative studies during the Pre-Treatment evaluation and/or during Treatment evaluation will not be considered a protocol deviation.

Correlative Study Collection Table 3

Procedures	**Pre Treatment**	**Cycle 1**											
	≤ 14 d prior to Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Cladribine Administration[A]		X	X	X	X	X							
Cytarabine Administration[A]		X	X	X	X	X	X	X	X	X	X		
Uproleselan Administration[B]		X	X	X	X	X	X	X	X	X	X	X	X
Bone Marrow Aspirate Collection (E-selectin Ligand Expression and RNA)	X												
Biomarker Collection (sE-selectin by ELISA)	X[C]	X[C,D]				X[E]					X[F]		X[G]

[A] Cladribine at the assigned dose level IV over approximately 1 to 2 hours, daily on days 1-5 combined with cytarabine at the assigned dose level SQ twice daily on days 1-10. The cytarabine should be administered approximately 3-6 hours following the start of the cladribine infusion.
[B] Uproleselan 800 mg IV on D1 and then IV Q12 hours on D2-12
[C] Pre-dose samples prior to Day 1 dosing; 2 sample collections - Screening and Baseline prior to dosing
[D] Day 1 sample – after uproleselan but prior to CLAD/cytarabine administration
[E] Day 5 sample after CLAD regimen administration
[F] Day 10 sample after cytarabine administration
[G] Day 12 after final uproleselan administration; 1 hour post last dose

E-selectin mediated interactions may play a role in AML and the expression of E-selectin or its binding epitope (sialyl Lea/x) may predict the clinical course and patient outcomes in AML. Increased expression of E-selectin, as seen in inflammatory conditions, malignant states such as leukemia, and during

chemotherapy, is also associated with increased shedding of E-selectin from the cell surface resulting in higher levels of sE-selectin in the circulation.

We will measure the levels of E-selectin ligand on pretreatment bone marrow blasts in patients treated with uproleselan to describe the cell-surface expression pattern of E-selectin ligand on AML blasts and to determine the effect on clinical outcomes. We will also examine plasma sE-selectin at baseline and after treatment with chemotherapy and uproleselan to determine if E-selectin inhibition affects sE-selectin levels and to correlate plasma levels with clinical outcomes.

We will measure the expression of E-selectin ligand-forming glycosylation genes from pretreatment bone marrow blasts treated with or without uproleselan to describe the RNA expression levels of these genes on AML blasts and to determine the effect on clinical outcomes.

E-selectin is a cell adhesion glycoprotein that is expressed on endothelial cells and has been implicated in therapeutic resistance. In most myeloid leukemias, leukemic blasts express E-selectin ligands, which contain the glycan epitope of the carbohydrate sialyl Le^x (sLe^x). This sequestration in the bone marrow vascular niche, leading to cell adhesion-mediated drug resistance and resultant poor clinical outcome. Uproleselan is an E-selectin antagonist which interrupts leukemic cell homing to the vascular niche, increases susceptibility to cytotoxic and targeted therapies and can be a potent adjunct to therapeutics. In deed data has demonstrated a correlation between leukemic cell surface levels of E-selectin ligands using multiparameter flow cytometry and response to uproleselan.

Recently, transciptome profiling of E-selectin ligand-forming glycosylation genes have been explored from public data sets to identify elevated E-selectin ligand expression in patients with AML. RNA-seq data from patients treated in COG AAML1031 (N = 1,074) was available for evaluation. Of 24 genes examined, Fucosyltransferase 7 (FUT7) and ST3 beta-galactoside alpha-2,3-sialyltransferase 4 (ST3GAL4) were significantly associated with adverse outcome (HR = 1.013, $p < 0.0001$, and HR = 1.023, $p < 0.0001$, respectively) and directly synthesize sLe^x. Patients highly expressing *FUT7* (highest quartile of expression) had significantly worse outcome than lower expressors (lowest 3 quartiles of expression), with a 5-year OS of 50.3% vs. 68.3% ($p < 0.0001$). Similarly, those with high *ST3GAL4* expression had a 5-year OS of 51.3%, compared to 68.1% for low expressors ($p < 0.0001$). High expression of these genes was shown to be associated with cell surface E-selectin ligand expression. Taken together these data suggest a strong correlation between transcriptome measurements of E-selectin ligand-forming glycosylation genes and cell surface glycosylation levels of E-selectin ligands, and lend support for the use of E-selectin ligand glycosylation genes as predictive biomarkers.

5.4.1 Soluble E-selectin Sampling and Processing

Care should be taken that blood for sE-selectin assessment is drawn from a vein apart from the site of investigational drug infusion (e.g., from a different limb or central line).

Blood (3-5 mL) will be drawn into sodium citrate tubes, inverted 3-4 times and stored in an ice bath until centrifugation. Samples will be centrifuged at 2000-2500 rpm at 4°C for 10 minutes. Ideally, samples should be immediately centrifuged following collection. If institutional staffing and/or logistics do not allow for this, samples may be stored (via an ice bath or at approximately 4°C) for 48-72 hours before centrifugation.

After centrifugation, pipette half of plasma into an appropriately labelled cryovial (primary aliquot). Pipette the remaining plasma into an additional appropriately labelled cryovials (back-up aliquot).

The aliquots will be stored in a freezer set at -70 to -80°C until shipped for analysis.

5.4.2 Soluble E-selectin Shipments

Samples will be shipped after each subject collection is complete. The primary and back-up aliquots will be shipped on separate days to mitigate loss (Monday - Wednesday only), via overnight carrier with the appropriate amount of dry ice.

QPS, LLC
ATTN Sample Coordinator
1 Innovation Way, Suite 200
Newark, Delaware 19711
Contact: Susan ZONDLO
E-mail: susan.zondlo@qps.com and tlmsmt@qps.com
Tel.: + 1 302 453 5911

Upon shipment of the samples, an e-mail will be sent containing a sample manifest, the name of the courier, the airway bill number, and a confirmation of the number of samples in the shipment.

5.4.3 E-selectin ligand/RNA Sampling and Processing

1. Perform bone marrow procedure, as per institutional procedure
2. Collect 2 ml bone marrow aspirate in a Sodium Heparin tube
3. Immediately after sample is drawn, gently invert the tube 180° and back, 8-10 times.
    a. Keep sample at AMBIENT TEMPERATURE

No additional specimen will be required for RNA testing. The sample collected for E-selectin ligand testing will provide sufficient material for RNA aliquoting.

5.4.5 E-selectin ligand Shipments

Samples should be shipped ambient on the day of collection.

Hematologics, Inc.

3161 Elliott Ave., Suite 200
Seattle, Washington 98121
Contact: Wayne Fritschle
E-mail: wayne@hematologics.com

Tel.: +1 8008600934 or +1 206 223 2700

Prior to shipping samples an email notification should be sent to laboratory@hematologics.com, including the protocol number, subject ID number and carrier tracking number.

5.5 Outside Physician Participation During Treatment

Interim visits can be provided by physicians outside MDACC. Additionally, in the event the patient cannot travel to MDACC for a new cycle visit, a telemedicine visit including laboratory review is acceptable and medications will be shipped directly to the patient. Local care for the patient includes routine blood work monitoring in between treatment cycles.

1. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to participate in the patient's care.

2. Protocol required evaluations outside MDACC will be obtained by 'Care Everywhere' in EMR, fax, or email. Records obtained via fax or email will be and scanned into the patient's record.

3. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator or their representative prior to initiation and documented in the patient record.

4. MDACC investigators will perform all decisions regarding dose adjustments and treatment interruptions or re-initiation of treatment, grading and attribution of adverse events, and assessment of efficacy. The home physician will not make any decisions regarding dose adjustments and/or treatment interruptions or resumption of treatment, grading and/or attribution of adverse events, or assessing efficacy. These will all be done by the MDACC investigators.

5. Routine, standard-of-care laboratory assessments (and physical exam when/if needed) will be performed by the home physician.

6. A copy of the informed consent and treatment schema will be provided to the local physician.

7. Documentation to be provided by the local physician will include drug administration records, vital signs, ECOG, concomitant medications, and progress notes, reports of the protocol required laboratory and diagnostic studies, and documentation of any hospitalizations.

8. The home physician will be requested to report to the MDACC physician investigator all life-threatening events within 24 hours of documented occurrence.

6.0 DOSING DELAYS / DOSE MODIFICATIONS FOR SUBSEQUENT CYCLES

6.1 Suggested dose levels for dose adjustments

Table 4

Dose level	Cladribine (mg/m^2 IV daily on days 1-5)*	Cytarabine (mg SQ twice daily on days 1-10)
1	5	20
-1	3.75	15
-2	2.5	10
-3	1.25	5

*3 days in consolidation

6.1.2. Dose levels different than dose described above may be allowed after discussion with the PI and documentation of the discussion.

6.1.3 Dose reductions for uproleselan are not planned. If there is a clinically significant grade 3 toxicity deemed related to uproleselan, it will be discontinued and patients will continue with chemotherapy alone.

Table 5

Non-Hematologic Toxicity	
Drug-related Grade 2 Toxicity Initiation of a treatment cycle will be delayed if a > Grade 1 non-hematologic toxicity has occurred or worsened and not yet returned to < Grade 2 prior to the start of the next cycle. Uproleselan will be discontinued in patients who experience a grade 2 or higher hypersensitivity reaction to the uproleselan. **Infection** If a patient develops a clinically significant infection of any grade,[1] initiation of treatment cycles may be delayed or withheld until the infection is clinically controlled (e.g., the patient is afebrile and with improving signs/symptoms). Treatment (i.e., subsequent cycles) may then resume at the full dose. At the discretion of the investigator, prophylactic therapy to prevent recurrence of infection can be instituted as clinically indicated.	
Description of Event: Non-Hematologic	**Dose Modifications**
Non-hematologic Grade 3 adverse event Drug-related grade 4 nausea, vomiting not optimally managed.	Hold therapy until recovery to Grade ≤1, then re-start and reduce one dose level. If toxicity recurs again, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -3 will be considered on an individual basis after discussion with the principal investigator.
For other grade 4 non-hematologic toxicity	Study drug should be discontinued
Persistent grade 2 toxicity considered clinically significant or upon patient's request	Consider holding therapy until recovery to Grade ≤1, then re-start and reduce one dose level. If toxicity recurs again, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -3 will be

	considered on an individual basis after discussion with the principal investigator.
Any occurrence of >/= drug related Grade 2 neurologic Events	The patient's study drug doses are to be re-evaluated in consultation with the Principal Investigator, and may be reduced according to the above parameters, or discontinued based on the event, and the time to resolution to ≤Grade 1.

[1] Includes, but is not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, *Pneumocystis carinii* pneumonia (PCP), disseminated *Varicella*, etc.

6.2 Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions implemented in subsequent cycles provided the toxicity has resolved as specified in the table above.

6.3 **Myelosuppression**: Patients with leukemias usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemias and myelodysplastic syndromes. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 weeks of therapy. After this time, treatment interruptions and dose adjustments may be considered according to the following guidelines:

6.3.1 Patients with neutropenia or thrombocytopenia as a consequence of the disease do not require treatment interruptions for myelosuppression. Dose-reductions in these patients should be considered in an individual case and discussed with the PI. The following guidelines can be used for these patients:

6.3.1.1 Patients with a response and pre-cycle counts of neutrophils >1 $x10^9$/L and platelets >50 $x10^9$/L who have sustained low counts of neutrophils <0.5 $x10^9$/L or a platelet count <20 x $x10^9$/L for more than 2 consecutive weeks in the current cycle, may receive a subsequent course at 1 dose level reduction. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

6.3.1.2 If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts, continue treatment regardless of neutrophil and platelet count and give supportive care as needed.

6.3.1.3 If no marrow evidence of leukemia, hold therapy until recovery of granulocytes to ≥1 $x10^9$/L and platelets ≥ 60 $x10^9$/L, then resume at same or 1 lower dose level according to guidelines mentioned above.

7.0 AGENT FORMULATION AND PROCUREMENT

Cladribine, and cytarabine are FDA approved and commercially available. Commercial supply will be used.

Uproleselan is an investigational agent and will be provided for the study by the manufacturer, GlycoMimetics. Expired or unused drug will be destroyed per institutional policy.

8.0 STATISTICAL CONSIDERATIONS

For Phase Ib, we will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al., 2016) to find the RP2D. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al., 2018).

The target toxicity rate is $\phi = 0.3$ and the maximum sample size is 12 for phase Ib. We will enroll and treat patients in cohorts of size 3. DLTs are defined in section 4.1.3, and only those DLTs that occur within **cycle 1** will be used for dose finding. The BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.236, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is ≥ 0.359, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.3 \mid \text{data}) > 0.95$ and at least 3 patients have been treated at dose level j, where p_j is the true DLT rate of dose level $j, j = 1, 2$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety.

The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 1, which will be used to conduct the trial. The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at dose level -1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1. When using Table 1, please note the following:
    a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the RP2D.

c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.

d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat step 2 until the maximum sample size of 12 is reached, or the trial is stopped early due to the elimination of the lowest dose.

Table 6. Dose escalation/de-escalation rule for the BOIN design

Number of patients treated at current dose	3	6	9	12
Escalate if # of DLT <=	0	1	2	2
De-escalate if # of DLT >=	2	3	4	5
Eliminate if # of DLT >=	3	4	5	7

Note. # of DLT is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of 3 patients.

When phase Ib is completed, select the RP2D based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the shiny app "BOIN" available at http://www.trialdesign.org. Specifically, select as the RP2D the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 30%. In addition, in order for a dose to be declared as RP2D, at least 6 patients have been treated with at least 80% of the planned doses and the observed DLT rate at the RP2D level is < 30% (for example, <=1 out of 6, or <=2 out of 7~9, etc.).

Operation Characteristics

Table 2 shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" available at http://www.trialdesign.org.

Table 7. Operating characteristics of the BOIN design

	1	2	Number of Patients	% Early Stopping
Scenario 1				
True DLT Rate	0.3	0.48		
Selection %	58.9	27.4		13.7
% Pts Treated	70.2	29.8	11.2	
Scenario 2				

True DLT Rate	0.16	0.3		
Selection %	27.4	71.3		1.3
% Pts Treated	48.5	51.5	11.9	
Scenario 3				
True DLT Rate	0.4	0.55		
Selection %	56.4	12.6		31
% Pts Treated	82.3	17.7	10.4	

For phase II portion, a maximum of 25 patients will be enrolled and treated at the RP2D level. The Bayesian approach of Thall, Simon, Estey (1995, 1996) will be used to monitor overall response (OR) and treatment-related toxicities. The OR is defined as either CR or CRi and the assessment window for OR will be 2 cycles. The toxicities to be monitored include those defined in section 4.1.2 which during cycle 1.

Based on published data, an overall response rate (ORR) of 35% is expected for this population and we aim to improve the ORR by 25%, that is to say, the target response rate would be about 45%, while maintaining the toxicity rate at or below 30%. With a sample size of 25 patients, the 95% posterior credible interval for ORR will range between 0.27 and 0.63, assuming an ORR of 45% (i.e., 11 out of 25 patients having responses) and a non-informative prior of beta (1, 1).

Denoting the historical probabilities of ORR and toxicity rate by {p(ORR,H) , p(TOX,H)}, the following monitoring rules will be applied:

1) Stop if Prob{p(ORR,H) + δ_{ORR} > p(ORR,E) | data} > 0.99, where δ_{ORR} = 0.1
2) Stop if Prob{p(TOX,H) < p(TOX,E)| data} > 0.95

where p(ORR, E) and p(TOX, E) are the true ORR and toxicity rates for the combination therapy. The priors of ORR and toxicities for the combination therapy are assumed to be Beta (1, 1) and Beta (0.6, 1.4), respectively. Patients will be monitored in cohort size of 5 according to the following stopping boundaries for ORR and toxicities.

Table 8: Stopping Boundaries for ORR and Toxicities, in cohort size of 5.

# Patients treated	Stop the trial if there are this many patients with CR/CRi:	Stop the trial if there are this many patients with toxicities:
5	never stop	4-5
10	0	6-10
15	0-2	8-15
20	0-3	10-20
25	Always stop with this many patients	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

Table 9: Operating Characteristics for toxicity and futility monitoring.

P(TOX)	P(ORR)	P(Stop Early)
0.20	0.25	0.30
	0.35	0.09
	0.45	0.03
	0.55	0.02
0.30	0.25	0.36
	0.35	0.17
	0.45	0.11
	0.55	0.10
0.40	0.25	0.53
	0.35	0.39
	0.45	0.34
	0.55	0.34
0.50	0.25	0.76
	0.35	0.69
	0.45	0.67
	0.55	0.66

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the operating characteristics table.

ANALYSIS PLAN

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The overall response rate will be estimated along with the 95% credible interval. Similar analyses will be performed for other binary outcomes such as CR, CRi, etc. Overall survival (OS) is defined as the time interval between treatment start and the date of death or last follow-up, whichever occurred first. Remission duration (CRd) is defined, within patients who achieve CR/CRi, the time interval between the date of CR/CRi and the date of disease relapse, death or last follow-up, whichever occurred first. Progression-free survival (PFS) is defined as the time interval between treatment start and the date of death, relapse or last follow-up, whichever occurred first. Kaplan-Meier method will be used to assess OS, CRd and PFS probabilities. Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v5.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency.

Cohort Summaries

The Investigator is responsible for completing toxicity summary reports and submitting them to the IND office Medical Affairs and Safety Group, for review and approval. These should be submitted as follows:

Phase 1B:
After the first 3 evaluable patients, complete cycle 1 of study treatment, and every 3 evaluable patients thereafter, prior to expanding/changing dose levels, or opening Phase II.

Phase II:
After the first 5 evaluable patients per cohort, complete cycle 2 of study treatment, and every 5 patients thereafter, until enrollment is complete.

A copy of the summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

9.0 MEASUREMENT OF EFFECT

9.1 Criteria for Response

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for response. Patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

9.1.2 Response Criteria

Response Criteria are according to the Revised Recommendations of the International Working Group Response Criteria in Acute Myeloid Leukemia. They are summarized below.

9.1.3 Complete remission (CR)

Disappearance of all clinical and/or radiologic evidence of disease, including extramedullary leukemia. Neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, and bone marrow differential showing $\leq 5\%$ blasts.

9.1.4 Complete remission without count recovery (CRi)

Have met all criteria for CR, except for either residual neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L).

9.1.5 **Complete remission with partial hematologic recovery (CRh)**

Having met all criteria for CR, but with only partial recovery of the peripheral blood count: ANC ≥ 0.5 x 10^9/L and platelets ≥ 50 x 10^9/L. (A subset of CRi)

9.1.6 **Partial remission (PR)**

Blood count recovery as for CR, but with a decrease in marrow blasts of at least 50% and not more than 6 to 25% abnormal cells in the bone marrow.

9.1.7 **Morphologic Leukemia-Free State (MLFS)**

Bone marrow differential showing < 5% blasts, no evidence of peripheral blasts or extramedullary disease, but without peripheral blood count recovery to neutrophil count ≥ 1.0 x 10^9/L & platelet count ≥ 100 x 10^9/L.

9.1.8 **Relapse-free survival (RFS)**

Time from CR or CRi until the date of first objective documentation of disease-relapse or death.

9.1.9 **Overall survival (OS)**

Time from date of treatment start until date of death due to any cause.

9.1.10 **Disease progression**

Progression will be defined as recurrence of the disease necessitating change in therapy, or failure to respond to therapy requiring change in treatment.

10. REGULATORY AND REPORTING REQUIREMENTS

10.1 Regulatory and Reporting Requirements

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTEP Version 5of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5 of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 5 of CTCAE.

Refer to Section 10.2 for Leukemia-Specific Adverse Event Recording Guidelines. AE data will be collected in Prometheus

10.2 Leukemia-specific Adverse Event Recording and Reporting Guidelines

Adverse Event Definition

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a medical treatment or procedure.

Definite - the adverse event is clearly related to the investigational agent(s).
Probable - the adverse event is likely related to the investigational agent(s).
Possible - the adverse event may be related to the investigational agent(s).
Unlikely - The adverse event is doubtfully related to the investigational agent(s).
Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

Adverse Event Severity

The severity of the adverse events (AEs) will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

Events not included in the NCI CTCAE will be scored as follows:

- Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
- Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- Grade 4: Life Threatening: discomfort that represents immediate risk of death

Adverse Events Recording:

These 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.
    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(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) 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.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Serious Adverse Event (SAE) Reporting Requirements

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor**.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the applicable Institutional Review Board (IRB) of record in accordance with their timeframes and procedures.
- Serious adverse events will be captured from the time of consent until 30 days after the last dose of drug or protocol specific timeline, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, including the development of new malignancies, must be reported to the IND/IDE Sponsor **within 24 hours of knowledge of the event** regardless of the attribution**.**
- Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the IND/IDE Sponsor. This may include the development of new malignancies.
- All events reported to the supporting company must also be reported to the IND/IDE Sponsor.

Reporting to FDA:
Serious adverse events will be reported to the FDA by the IND/IDE Sponsor according to 21 CFR 312.32. For SAEs determined by the IND Sponsor to meet the criteria for prompt reporting to the FDA, the principal investigator will be provided with a MedWatch form. The completed MedWatch form must be returned to the IND Sponsor by the due date specified by the IND Sponsor.
It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the IND/IDE sponsor's guidelines, and Institutional Review Board policy.

Reporting of Serious Adverse Events to GlycoMimetics
All SUSARs occurring during the Study should be reported to GlycoMimetics with a Completed Regulatory Form (Institution's eSAE form) for initial and follow-up in parallel with submission to the FDA for patients exposed to GMI product by email to (Safety-inbox.biotech@iqvia.com) . All serious adverse events and follow-up occurring during the Study should also should be reported within 15 days post-Sponsor awareness date for patients exposed to GMI product by email to (Safety-inbox.biotech@iqvia.com).

11.0 DATA SECURITY/CONFIDENTIALITY

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

Access to Study Records

Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Methods of Storage of Study Records

All data collected from MD Anderson Cancer Center (MDACC) sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient- investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared. Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors.

Duration of Study Record Storage

The study participant's contact information will be securely stored at each clinical site for

internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Sharing of Study Records

There are no plans to share study identifiable data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

12.0 STUDY OVERSIGHT

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician always have access to the data.

Required: All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.1 Data and Safety Monitoring

Data and Safety Monitoring is the process for reviewing data collected as research progresses to ensure the continued safety of current and future participants as well as the scientific validity and integrity of the research. Studies conducted at MD Anderson will follow the DSMP that has been approved by the NCI.

The Principal Investigator is ultimately responsible for the conduct and monitoring of all aspects of the study on an ongoing basis. The Principal Investigator will provide an annual review and report of the study, including all adverse events, accrual information, efficacy and response data, along with overall study progress and continuation plans to MD Anderson's Data and Safety Monitoring committees responsible for study oversight.

For this study, MD Anderson's Data and Safety Monitoring Committee is responsible for study oversight.

12.2 Clinical Trial Monitoring

Regular monitoring of trial conduct will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

12.3 Consent Process and Documentation

This protocol will follow the SOP 04_Informed Consent Process. SOP 04 has been read by the research staff and investigators. Informed consent may be obtained using the following methods: Remote consent, In-person consent.

13.0 STATEMENT OF COMPLIANCE

Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation.

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