Protocol Title: A Randomized, Phase II Study of CX-01 Combined With Standard Induction Therapy for Newly Diagnosed Acute Myeloid Leukemia

Protocol Number: CNTX-CX-01-2015-AML-1 (NCT02873338)

Protocol Date: 04 February 2016
Amendment 1: 16 September 2016
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Clinical Study Protocol

Protocol Title: A Randomized, Phase II Study of CX-01 Combined With Standard Induction Therapy for Newly Diagnosed Acute Myeloid Leukemia

IND Number: 118 960
Product: CX-01 (2-O, 3-O desulfated heparin; ODSH)
Protocol No.: CNTX-CX-01-2015-AML-1
Phase: II

Prepared for:

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Final Protocol incorporating Amendment 2: JANUARY 13, 2017

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SYNOPSIS

Study Number:	CNTX-CX-01-2015-AML-1
Title of Study:	A Randomized, Phase II Study of CX-01 Combined With Standard Induction Therapy for Newly Diagnosed Acute Myeloid Leukemia
Indication:	Newly diagnosed acute myeloid leukemia (AML)
Number of Investigators and Study Centers:	The study will be conducted at approximately 25 sites in the United States.
Development Phase:	Phase II
Objectives:	**Primary objectives** The primary objectives are: • To assess whether 2-O, 3-O desulfated heparin (CX-01), administered at any or all studied dose levels in conjunction with standard induction therapy for AML increases the morphologic complete remission (CR) rate based on International Working Group (IWG) criteria • To assess the safety and tolerability of CX-01, administered at two studied dose levels in conjunction with standard induction therapy for AML. **Secondary objectives** The secondary efficacy objectives are: To assess whether CX-01, administered at any or all studied dose levels in conjunction with standard induction and consolidation therapy for AML improves: • Event-free survival (EFS) • Leukemia-free survival (LFS) • Overall survival (OS) • Composite CR rate: incidence of CR + CRi, which is CR without recovery of neutrophils and/or platelets (ANC may be <1000 μL and/or platelet count <100,000/μL). • Duration of morphologic CR • 30-day mortality (in the induction cycle) • 60-day mortality (in the induction cycle) • 90-day mortality (in the induction cycle) • Neutrophil recovery • Platelet recovery.
Study Population:	Newly diagnosed, treatment-naïve patients with de novo or secondary AML 60 years of age or older.
Methodology/ Study Design:	This is an exploratory phase II, open-label, randomized, multicenter, parallel group trial to determine whether there is evidence that the addition of either or both different dose levels of CX-01 to standard induction and consolidation chemotherapy has an additive therapeutic effect in newly diagnosed AML patients when compared to patients receiving standard induction chemotherapy alone. Patients will be randomized in a 1:1:1 ratio to receive standard induction and consolidation chemotherapy plus lower or higher dose CX-01 or standard induction and consolidation chemotherapy alone. During long term follow-up, relapse and OS data will be collected every 3 months until death or until the end of study. The end of study will occur approximately 18 months after the last patient is randomized.

	A Data and Safety Monitoring Committee will meet periodically to review the safety of the study. Adverse events (AEs) will be collected from time of informed consent and continue until 30 days after last study treatment is administered. Longer follow-up and collection of AEs may be required for patients who do not have an absolute neutrophil count (ANC) recovery by Day 42 (i.e. until the recovery or until the reason for no recovery is diagnosed) after the last induction or consolidation cycle.
Number of Patients (planned and analyzed):	Approximately 75 patients
Study Medications:	**Group 1:** Idarubicin + Cytarabine, OR **Group 2:** Idarubicin + Cytarabine + plus lower dose CX-01 (0.125 mg/kg/hour), OR **Group 3:** Idarubicin + Cytarabine + plus higher dose CX-01 (0.25 mg/kg/hour)
Dose regimen:	For induction therapy, all patients will receive standard idarubicin + cytarabine chemotherapy. Patients randomized to Groups 2, and 3 will also receive CX-01. CX01 will be continually infused while idarubicin will be administered per institutional standards. Patient will be randomized to one of the following treatment groups: **Induction therapy:** **Group 1: Idarubicin + Cytarabine** • Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) intravenous (IV) injection/infusion daily on Days 1, 2, and 3 • Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7. **Group 2: Idarubicin + Cytarabine + plus lower dose CX-01** • CX-01 given as a 4 mg/kg initial bolus on Day 1 only, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-7 • Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3 • Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7. **Group 3: Idarubicin + Cytarabine + plus higher dose CX-01** • CX-01 given as a 4 mg/kg initial bolus on Day 1 only, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-7 • Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3 • Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7.

Re-induction therapy
Patients who do not achieve leukemia-free state (<5% bone marrow blasts) on bone marrow aspirate performed between Days 14-21 may receive a re-induction cycle with the same regimen ("7 + 3" ± CX-01) as outlined above.

If, in the Investigator's opinion, the patient is not fit to receive full re-induction cycle of "7 + 3" ± CX-01, at the Investigator's discretion the patient may receive "5 + 2" ± CX-01 which is 5 days of cytarabine and 2 days of idarubicin ± CX-01 as outlined below:

Group 1: Idarubicin + Cytarabine
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Group 2: Idarubicin + Cytarabine + plus lower dose CX-01
- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Group 3: Idarubicin + Cytarabine + plus higher dose CX-01
- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Consolidation therapy
If there are <5% bone marrow blasts in the bone marrow aspirate performed between Days 14-21, a second bone marrow aspiration will be performed within 1 week after ANC recovers to >1000/μL. If CR is documented, and depending on factors including, but not limited to, European Leukemia Net genetic risk and co-existing conditions, patients may proceed to consolidation (if not proceeding to transplant). Patients who are not in CR at the end of re-induction will be taken off study and will complete Early Termination Visit.
During consolidation, patients will continue in the same treatment group as assigned at randomization as follows:

Group 1: Cytarabine
- Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.

Group 2: Cytarabine + lower dose CX-01
- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of the first 3-hour infusion of cytarabine, followed immediately by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5 for a total of 120 hours of continuous CX-01 infusion

	• Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5. **Group 3: Cytarabine + higher dose CX-01** • CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of the first 3-hour infusion of cytarabine, followed immediately by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5 for a total of 120 hours of continuous CX-01 infusion • Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.
Duration of Treatment:	Patients will receive up to two induction cycles and up to two consolidation cycles of treatment.
Duration of Patient Participation in Study:	Each patient will participate in the study for approximately 18 months from the time of informed consent through final study contact, or until they withdraw from the study or the study is terminated by the Sponsor.
Diagnosis and Main Criteria for Inclusion:	To be eligible to participate in the study, patients must meet the following criteria: 1. Newly diagnosed, *de novo* or secondary, previously untreated AML 2. Age 60 or above 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 4. Cardiac ejection fraction ≥45% (as determined by echocardiography or multi gated acquisition scan) 5. Adequate hepatic and renal function determined by the following laboratory values: • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 x upper limit of normal (ULN) • Bilirubin <2.5 x ULN • Calculated creatinine clearance by Cockcroft Gault formula >30 mL/min. 6. Able to provide informed consent and have signed an approved consent form that conforms to federal and institutional guidelines.

Exclusion Criteria:	Patients who meet any of the following criteria will not be eligible to participate in the study: 1. Patients with acute promyelocytic leukemia based on the presence of t(15;17)(q22;q12) as determined by karyotyping, fluorescence in situ hybridization or polymerase chain reaction 2. Prior chemotherapy for AML (including investigational therapy); prior hydroxyurea to control white blood cell count and a single intrathecal administration of cytarabine for CNS prophylaxis is allowed 3. Prior intensive chemotherapy or stem cell transplantation for treatment of myelodysplastic syndrome (prior treatment with hypomethylating agents and lenalidomide are allowed) 4. Presence of central nervous system leukemia 5. Presence of significant active infection that is not controlled in the opinion of the Investigator 6. Presence of significant active bleeding 7. History of severe congestive heart failure or other cardiac disease that contraindicates the use of anthracyclines, including idarubicin 8. Pre-existing liver disease (such as CHILD-Pugh Class B or C liver disease) 9. Renal insufficiency which might adversely affect schedule and dose of therapy with cytarabine as well as management of tumor lysis syndrome 10. History of drug addiction within the last 6 months 11. Known history of positive Hepatitis B surface antigens 12. Known history of positive test for Human Immunodeficiency Virus antibodies 13. Psychiatric or neurologic conditions that could compromise patient safety or compliance, or interfere with the ability to give proper informed consent 14. History of other active malignant disease within the past 3 years, other than cured basal cell carcinoma of the skin, cured in situ carcinoma of the cervix, or localized prostate cancer that has received definitive therapy. Such prostate cancer patients who are receiving hormonal therapy are eligible 15. Patients receiving any form of anticoagulant therapy (heparin flushes for IV catheter permitted) 16. Presence of a known bleeding disorder or coagulation abnormality (including but not limited to a PTT >40 seconds) or any condition that requires maintenance of platelet counts at 50,000/μL or higher 17. Pregnant or breast feeding patients 18. Patients of childbearing potential not using adequate contraception.

Evaluation: Efficacy	Bone marrow aspiration will be done between Days 14-21. If LFS is documented, an aspirate will be repeated within 1 week after the ANC recovers to >1000/μL. Bone marrow aspirate will also be repeated approximately 42 days after of initiation of the induction cycle for patients who do not have recovery of ANC. Response will be evaluated based on IWG criteria. For patients with documented CR, confirmatory bone marrow aspirate slides will be submitted to the Sponsor or designee. **Primary efficacy endpoint** The primary efficacy endpoint is the morphologic CR rate based on IWG criteria. **Secondary efficacy endpoints** The secondary endpoints are: • EFS • LFS • OS • Composite CR rate: incidence of CR + CRi • Duration of morphologic CR • 30-day mortality • 60-day mortality • 90-day mortality • Time to neutrophil recovery defined as days from the date of randomization until ANC recovered to >1000/μL • Time to transfusion-independent platelet recovery defined as days from the date of randomization until the first day that the platelet count recovers to >100,000/μL (provided it is not as a consequence of platelet transfusion and provided platelets are then maintained at >100,000/μL for the five subsequent days without platelet transfusion).
Evaluation: Safety	Key safety endpoints will be assessed by review of summaries of AEs which will include only treatment-emergent adverse events (TEAEs), unless otherwise stated. Adverse events will be categorized by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 14.1), and will be graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Statistical Methods:	Sample Size A total of 25 evaluable patients per arm will provide 71.8% power for each test comparing a dose with control via a Fisher's exact test at 1-sided alpha = 0.15 to detect a difference between a control proportion 0.55 and an experimental dose proportion 0.80; these tests will be conducted in a fixed sequence: higher dose versus control first and lower dose versus control second, with the second test considered exploratory (failed) if the first test fails. **Analysis populations** The following populations will be considered for data summaries. Intent-To-Treat (ITT): All randomized patients. Patients will be analyzed according to the treatment to which they are randomized. The ITT Population will be the primary analysis set for the efficacy variables. Per Protocol (PP): Supporting analyses will be conducted on the PP Population, comprising all patients randomized and treated without major protocol violations during the trial. This population will be documented before final database lock. Safety: All patients who received at least one dose of study treatment. Patients will be included in the analyses according to the treatment they received. The Safety Population will be used in the analyses of all safety endpoints. **Primary analysis** The primary efficacy analyses will be based on the ITT Population. Fisher exact test will be used to compare the proportion of CRs between each dose and control. **Secondary analysis** The primary analysis will be repeated using the PP Population as a supportive analysis. Complete response rates and confidence intervals will also be reported for key subgroups (e.g., randomization strata). Analyses of EFS, LFS, time to neutrophil recovery, time to platelet recovery, and OS will be descriptive. Kaplan-Meier (KM) estimates will be used to estimate the survival distribution for each arm and KM plots will be produced to accompany these analyses. Confidence intervals will be reported for medians and KM estimates. Duration of response will be analyzed using a similar approach; the analysis will account for the competing risk of death and the survival distributions will be estimated as cumulative incidence functions. Mortality rate at Day 30, Day 60, and Day 90 will be reported using descriptive statistics in a manner similar to the reporting of the morphologic CR rate. The time to neutrophil and platelet recoveries will be reported using the following descriptive statistics: N, mean, standard deviation, median, minimum, maximum, and 1st and 3rd quartiles.

Statistical Methods:	**Exploratory analysis** Exploratory analyses will be descriptive. **Safety analysis** Safety analysis will be descriptive, based on the Safety Population and will involve examination of descriptive statistics and individual patient listings for effects of study treatment on clinical safety and tolerability. The safety assessment period is from the first dose of study treatment until 30 days following the last dose of study treatment. All AEs will be categorized by SOC and Preferred Term using MedDRA dictionary and graded according to NCI-CTCAE v4.03. Treatment-emergent AE summaries will include NCI-CTCAE Grade 3 or higher AEs, and AEs resulting in discontinuation of study treatment, AEs resulting in death, deaths during the treatment period within 30 days of the last study treatment, deaths reported beyond 30 days that are considered study drug-related, and the incidence of laboratory values with NCI-CTCAE Grades 3 or 4. Particular attention will be upon coagulation parameters and bleeding-related events. Vital signs and ECOG performance status, electrocardiograms, and laboratory parameters will be summarized descriptively. **Pharmacokinetic analysis** Pharmacokinetic analyses will be descriptive.

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1. INVESTIGATOR/SPONSOR AGREEMENT

This protocol was designed and will be conducted, recorded, and reported in accordance with the principle of Good Clinical Practice (GCP) as stated in the International Conference of Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws. I have read and agree to abide by the requirements of this protocol.

_____ _____

Principal Investigator Date

Sponsor Signature:

_____ _____

Stephen Marcus, M.D. Date
Chief Executive Officer
Cantex Pharmaceuticals, Inc.

2. LIST OF ABBREVIATIONS

Table 2—1: List of Abbreviations

Abbreviation	Definition
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-factor Xa	anti-factor10a
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CAF	cancer-associated fibroblast
CIT	chemotherapy-induced thrombocytopenia
COPD	chronic obstructive pulmonary disease
CR	complete remission
CRi	complete remission without recovery of neutrophils and/or platelets
CRO	contract research organization
CRp	complete remission without recovery of platelets
CSA	clinical study agreement
CSR	clinical study report
CX-01	2-O, 3-O desulfated heparin (ODSH)
D	day
Disc.	discontinuation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELN	European Leukemia Net
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
cGMP	current Good Manufacturing Practice
HIT	heparin-induced thrombocytopenia
HSC	hematopoietic stem cells
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference of Harmonisation
IND	Investigational New Drug
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	intravenous
IWG	International Working Group
IxRS	Interactive Web/Voice Response System
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFS	leukemia-free state
LFT	liver function test
LMWH	low molecular weight heparin
LSC	leukemic stem cells
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multi gated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ODSH	2-O, 3-O desulfated heparin
OS	overall survival
PF4	platelet factor 4
PFS	progression-free survival
PLE	protein losing enteropathy
PP	Per Protocol
PT	prothrombin time
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	standard deviation
SOC	System Organ Class
SUSAR(s)	suspected unexpected serious adverse reaction(s)
TEAE(s)	treatment-emergent adverse event(s)
UFH	unfractionated heparin
ULN	upper limit of normal
WBC(s)	white blood cell(s)
WHO-DD	World Health Organization Drug Dictionary

3. ETHICAL CONSIDERATIONS

3.1 Institutional Review Board

The protocol and informed consent form (ICF) will be reviewed and approved by the Institutional Review Board (IRB). The Sponsor will supply relevant material for the Investigator to submit to the IRB for the protocol's review and approval. Documentation of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator.

The Investigator must submit and, where necessary, obtain approval from IRB for all subsequent protocol amendments. Approval for protocol amendments will be transmitted in writing to the Investigator. If requested, the Investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB with progress reports at required intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

3.2 Ethical Conduct of the Study

The study procedures outlined in this protocol will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH consolidated Guideline E6 for GCP, and the applicable national/regional laws and regulatory requirement(s).

3.3 Patient Information and Consent

Written informed consent for the study will be obtained from all patients before any protocol-specific procedures are conducted. The ICF generated by the Sponsor or designee will be approved (along with the protocol) by the IRB.

Information about the study will be given to the patient both verbally and in writing. The written patient information sheet will explain the objectives of the study and its potential risk and benefits. The patient should have adequate time to read the information sheet and to ask the Investigator any questions. The Investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient should not enter the study.

If a patient agrees to participate, he/she will be asked to sign and date the study ICF which will be retained by the Investigator. A copy of the signed ICF will be given to the patient. The informed consent process must be documented in the patient's source documents. The original ICF must be retained by the Investigator and made available for inspection by the Study Monitor.

4. INTRODUCTION

This is a phase II study to evaluate 2-O, 3-O desulfated heparin (CX-01), a low molecular weight heparin (LMWH) derivative with inhibitory effects on the CXCL12/CXCR4 axis, a pathway that has been shown to be important in cancer stem cell survival, proliferation, migration, and chemotaxis. It is proposed that the addition of CX-01 at two dose levels to idarubicin + cytarabine may be of benefit in the treatment of acute myeloid leukemia (AML).

At present, CX-01 has been administered to 189 adults and children in phase I and II trials in which a highly favorable safety profile was observed.

4.1 Background Information

Heparin was discovered almost 100 years ago (1), and through most of its life has been employed as an anticoagulant to treat or prevent vascular thrombosis. However, because of heparin binding motifs on a host of proteins, this glycosaminoglycan has multiple pharmacologic effects that are not dependent upon anticoagulation (2). In cancer, these non-anticoagulant actions, and most notably its ability to disrupt the CXCL12/CXCR4 axis, offers an intriguing set of therapeutic possibilities for using heparin as adjunctive treatment to conventional therapy. These therapeutic possibilities are, however, severely limited by unacceptable anticoagulant effects at heparin doses required for relevant non-anticoagulant pharmacologic activity. This observation led to the development of a low anticoagulant CX-01 that retains the broad range of biologic activities of heparin, with only a small fraction of its anticoagulant activities.

Acute myelogenous leukemia afflicted 18,860 patients in the United States in 2014 and resulted in 10,460 deaths. Despite incremental advances (3,4), the mainstay of AML induction therapy continues to be variations on a 7-day infusion of cytarabine and 3 days of an anthracycline (“7 + 3”), an approach three decades old (5). Relapses are believed to be due to quiescent $CD34^{+}CD38^{-}$ leukemic stem cells (LSCs) nestled in the marrow stromal niche, where they are resistant to the cytotoxic effects of chemotherapy.

4.1.1 The CXCL12/CXCR4 Axis in Cancer Biology

The CXCL12/CXCR4 axis has recently been suggested as a new therapeutic target in lung cancer (6,7). CXCL12 (also known as Stromal Cell Derived Factor-1) was first described as a CXC chemokine produced locally within the bone marrow compartment that provides a homing signal for hematopoietic stem cells (HSCs) by ligation of its G-protein coupled receptor (CXCR4) to the surface of HSCs. Ligation of CXCR4 activates a number of signaling pathways, in particular the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which promotes stem cell survival, proliferation, migration, and chemotaxis (7).

More recently, it has been appreciated that splice variants of CXCL12 are also produced in high concentrations in brain, lung, colon, heart, kidney and liver, and that these CXCR4 receptors are prominently expressed on the cell membranes of many cancer cells,

particularly cancer stem cells (7). This emerging research supports a role for the CXCL12/CXCR4 axis in mediating the invasion/migration by cancer cells and cancer stem cells into the "fertile soil" sites commonly associated with metastasis. Thus, it is proposed that local production of CXCL12 within metastasis-prone sites promotes the chemotaxis of cancer cells and cancer stem cells into these sites through interaction with the CXCR4 on the membranes of cancer cells.

In addition, the CXCL12/CXCR4 axis appears to be important in cancer cell proliferation and neovascularization, and is intimately involved in recruiting cancer-associated fibroblasts (CAF) that provide the mesenchymal matrix support for growing tumors and further metastases (7). Thus, a major promoter of CXCL12 and CXCR4 expression within a tumor is its hypoxic core, which gives rise to hypoxia inducible factor 1α. CXCL12 is also produced abundantly by CAFs and inflammatory macrophages within the tumor. Once stimulated by CXCL12, tumor cell associated CXCR4 becomes a major mediator of tumor cell interaction with extracellular matrix proteins (i.e., laminin, fibronectin, collagen), as well as a regulator of CD44 and integrin-mediated cancer and cancer stem cell adhesion (though CXCR4 itself is not directly involved in cell adhesion).

4.1.2 The CXCL12/CXCR4 Axis in Acute Myeloid Leukemia

Normal $CD34^{+}CD38^{-}$ HSCs migrate to and are anchored in the bone marrow by chemotactic signals produced by cells in the marrow stroma (8,9,10,11). Foremost of these signals is the CXC chemokine CXCL12 (stem cell derived factor-1), which ligates chemokine receptor 4 (CXCR4) on the HSC surface. This signaling activates directional Rho/Rac-mediated migration toward and attachment in the bone marrow environment through enrichment of pseudopodia with adhesion receptors such as very late antigen-4 and others. CXCL12/CXCR4 signaling also activates phosphatidylinositol-3-kinase and its downstream effector protein kinase B, providing enhanced survival (10). In the marrow, HSCs shuttle between an endosteal osteoblastic niche inducing quiescence and a sinusoidal endothelial vascular niche promoting proliferation and differentiation (8). Recent evidence suggests that quiescence in the endosteal niche is maintained by close association with megakaryocytes (12,13). Megakaryocytes negatively regulate HSC proliferation through secretion of platelet factor-4 (PF4), which also enhances integrin-mediated endothelial adhesion during bone marrow homing (14).

There is substantial evidence that LSCs employ the same CXCL12-, CXCR4-, adhesion molecule-dependent mechanisms as normal HSCs to home toward a marrow niche and maintain themselves in a quiescent, protected state (8,14,15,16,17,18,19,20,21,22,23). CXCR4 is an unfavorable prognostic marker in AML (24,25,26,27,28), and its high expression on $CD34^{+}$ AML is associated with the poor survival in patients with Fms-like tyrosine kinase-3 /internal tandem duplication mutations. Conversely, disrupting CXCR4 signaling inhibits transmigration, survival and chemotherapy resistance *in vitro* (29,30,31,32) and tumor growth in AML xenografts (32,33,34,35). Clinical experience with the CXCR4 inhibitor Plerixafor in AML is just beginning (36,37). Short term daily subcutaneous administration of Plerixafor for up to 7 days for stem cell mobilization is well tolerated (38). However, cardiac toxicity arose when it was administered as a daily intravenous (IV) infusion or subcutaneous injection for 11-14 days (39). This questions

the safety of long term continuous blockade of CXCR4, a receptor also important in repair of injured tissues.

An alternative approach to blocking CXCR4 signaling is direct interference with its ligand CXCL12. Heparin, a glycosaminoglycan used as an anticoagulant, avidly binds to a cluster of cationic amino acids on the CXCL12 surface that overlaps with the CXCR4 binding region (40,41). Heparin inhibition of CXCL12 is diminished by removal of 6-O, but not 2-O sulfates (42), but is apparent only at concentrations of 20 U or approximately 3 μg/mL (42,43), which exceed therapeutic heparin plasma levels for anticoagulation by 10-fold (44). Low anticoagulant 2-O, 3-O desulfated heparin (ODSH, also known as CX-01, Figure 6—2) is a porcine intestinal heparin derivative that retains many heparin anti-inflammatory properties. Additionally, CX-01 binds PF4 with affinity similar to heparin, but the CX-01/PF4 complex does not bind antibodies that produce platelet activation and mediate heparin-induced thrombocytopenia (HIT). Furthermore, megakaryopoiesis is negatively regulated by PF4 and anti-PF4 blocking antibodies diminish chemotherapy-induced thrombocytopenia (CIT) in mice. CX-01 binds to and reverses biologic activities of PF4 and mitigates CIT in transgenic mice that overexpress PF4.

Based on these considerations, we conducted a pilot study combining CX-01 with standard chemotherapy for the treatment of AML. Results, as described below, suggest that CX-01 increases the complete remission (CR) rate and enhances count recovery. In addition, we show that CX-01 potently inhibits CXCL12 ligation of CXCR4 *in vitro* at concentrations that do not produce anticoagulation.

4.1.3 Clinical Strategies to Block CXCR4

A number of strategies have been tested to block CXCR4, among these are AMD3100 (Genzyme), BKT140 (Biokine Therapeutics), MSX-122 (Med Koo Biosciences), unfractionated heparin (UFH) and LMWH (various).

AMD3100 (known as Plerixafor and Mozobil), has gained Food and Drug Administration approval for the mobilization of stem cells. AMD3100, when used with another small molecule CXCR4 inhibitor, BKT140, acts synergistically with chemotherapy in human non-small cell lung cancer under experimental conditions (45,46,47) as well as against small cell lung cancer (SCLC) in vitro and in animal models (48,49,50,51).

Short term daily subcutaneous administration of AMD3100 for up to 7 days in humans for stem cell mobilization is well tolerated (52), but when administered as a daily IV infusion or subcutaneous injection for 11-14 days, as an HIV treatment in humans, it was associated with cardiac toxicity (53,54). MSX-122, also developed for stem cell mobilization, is a partial CXCR4 antagonist which in animal studies appears to be tolerated in longer term regimens, however, MSX-122 has not as yet been tested in humans.

Heparins are effective inhibitors of CXCL12. Recently, UFH has been shown to inhibit CXCL12 in a manner not dependent on its anticoagulant activity (42). Binding of heparin

produces a steric hindrance of CXCR4 binding to CXCL12 (55) when this negatively charged glycosaminoglycan binds to a concentration of cationic amino acids that overlap with the CXCR4 binding site (55). However, even greater effectiveness might be achieved using, CX-01, a low anticoagulant heparin, that would enable effective CXCL12 blocking without the risk of anticoagulation.

4.2 Study Rationale for CX-01 in AML

CX-01 is a rationally engineered complex carbohydrate derived from heparin that may represent a safer inhibitor of the CXCL12/CXCR4 axis.

Differential anticoagulant effect relative to heparin: Heparin is more than 200 fold more potent than CX-01 as an anticoagulant. The anticoagulant effect of CX-01 begins to appear at a plasma concentration that is approximately 2-fold higher than the plasma concentrations achieved in normal volunteer and patient studies (25 μg/mL); at these concentrations it is anticipated that CX-01 can be employed clinically with little if any anticoagulant effect (56).

Reduced antigenicity relative to heparin: HIT is a potential clinical complication of heparin administration that results from the formation of an antibody to the PF4/heparin complex, which in turn may cause thrombocytopenia and thromboembolism (57). CX-01 binds PF4 with an affinity similar to heparin, but the CX-01/PF4 complex does not activate platelets because it does not bind HIT antibodies and, unlike heparin/PF4, does not stimulate additional antibody production (56,58,59).

Platelet and white blood cell (WBC) recovery following chemotherapy: In patients with metastatic pancreatic cancer receiving gemcitabine + *nab*-paclitaxel, and in patients with AML receiving induction therapy with idarubicin and cytarabine, CX-01 appears to accelerate both platelet and WBC recovery after high dose chemotherapy. The acceleration of platelet and WBC recovery may be explained by a blocking effect of CX-01 on the inhibitory action of PF4 in marrow myeloid and megakaryocyte development after chemotherapy (60,61,62). In separate but related research, Cantex is collaborating with the National Institute of Health and other federal agencies to develop CX-01 as a medical countermeasure to radiation poisoning, where refractory thrombocytopenia is a major concern.

Thus, CX-01 may offer benefits to AML patients without the risks of other heparin derivatives, namely blocking of the CXCL12/CXCR4 axis without the accompanying risks of anticoagulation or of HIT; it may also benefit AML patients receiving intensive chemotherapy by accelerating platelet and WBC recovery times.

4.3 Summary of Studies with CX-01

4.3.1 Preclinical Data

In rats the no-observed-adverse-effect-level (NOAEL) was 48 mg/kg/day, and in dogs it was 160 mg/kg/day. The only observed adverse effect in either species was the expected

occurrence of hemorrhage at high doses of drug, when coagulation parameters were prolonged. No adverse effect on cardiac conduction has been observed in porcine studies of myocardial infarction. There were no adverse effects of CX-01 administration on the cardiovascular profile in dogs or on the respiratory parameters in albino rats.

4.3.2 Clinical Data

As of October 9, 2015, a total of 188 patients had been exposed to CX-01 at doses of 4 to 20 mg/kg as a bolus and doses of 0.125 to 3.9 mg/kg/hour as a continuous IV infusion for durations of 12 to 168 hours.

- 54 healthy subjects who participated in three phase I trials
- 78 subjects with exacerbation of chronic obstruction pulmonary disease (COPD) in a phase II study
- 35 patients with metastatic pancreatic cancer
- 5 patients with exacerbation of protein losing enteropathy (PLE) secondary to Fontan procedure (phase II study)
- 12 patients with AML
- 4 pediatric patients with recurrent solid tumors.

Table 4—1 Clinical Data in Conditions Other than Acute Myeloid Leukemia

Study Number	Phase	Indication	Number of Patients	Study Drug and Dose	Study Endpoints	Study Results
PGX-ODSH-2013-AML-1	Pilot	AML	N=12	Cytarabine at 100 mg/m^2/day as a continuous infusion for 7 days; Idarubicin 12 mg/m^2 daily for 3 days; CX-01 given as a 4 mg/kg bolus followed by 6 mg/kg/day as a continuous infusion for 7 days (168 hours)	Primary • Safety and tolerability of CX-01 when combined with chemotherapy • Obtain preliminary evidence of the effect of CX-01 on platelet transfusion independence Secondary Effect of CX-01 on CR rate, platelet nadir count, number of platelet transfusions, induced side effects	Combination was associated with CR rate of 92%. Hematologic recovery was rapid. Even though a small population was treated, data suggests that CX-01 could not only be a chemotherapy sensitizer for traditional 7+3 induction therapy but could also accelerate count recovery after induction. CX-01 was found to be safe and well tolerated with no unexpected SAEs.
PGX-ODSH-2006	II	Exacerbation of COPD	N=156, equally randomized to receive standard treatment of COPD with or without CX-01	CX-01 given as a 8 mg/kg bolus followed by CX-01, 0.375 mg/kg/h for 96 hours	Primary Composite of failure to discharge from hospital in a timely manner + relapse within 21 days of hospital discharge Secondary FEV_1, FEV_1/FVC, Borg CR10Scale, 6-minute Walk Test, BODE index and hs-CRP	There was no evidence of effect or efficacy of CX-01 compared to placebo for the primary endpoint for Intent-to-Treat (ITT) or Per Protocol (PP) Populations. No statistical significant effects were shown for the secondary endpoints. CX-01 was well tolerated. A few instances of minor/moderate bleeding and only one case of major bleeding. Some predictable changes were noted for AST and ALT with CX-01 treatment. No other clinical and laboratory parameters showed

Study Number	Phase	Indication	Number of Patients	Study Drug and Dose	Study Endpoints	Study Results
						significant changes from baseline. Eight deaths were reported (placebo=5 and CX-01=3). Those three were not related to CX-01 occurred post treatment.
PGX-ODSH-2009-PLE	II	Protein losing enteropathy (PLE) secondary to Fontan procedure	N=5, Pediatric and young adult population	CX-01, 96 hour IV infusion at 0.125 mg/kg/h or CX-01, 96 hour IV infusion at 0.250 mg/kg/h	Safety, reduction of symptoms of PLE, reduction of alpha-1 antitrypsin levels	Though all patients had some subjective clinical improvement, CX-01 did not show clear effects on efficacy biomarkers. Due to extremely low patient enrollment and a lack of efficacy, the study was terminated early. 22 AEs and two unrelated SAEs were reported. All AEs were considered mild or moderate in intensity.
PGX-ODSH-2011-PC	II	Metastatic pancreatic cancer	N=60, with 35 patients receiving CX-01 in conjunction with chemotherapy and 25 randomized to receive chemotherapy alone	Gemcitabine (1000 mg/m^2) and *nab*-paclitaxel (125 mg/m^2) on days 1, 8, and 15 for 3 weeks with or without CX-01 (4 mg/kg bolus followed by CX-01, 0.375 mg/kg/h for 48 hours) starting with the first dose of chemotherapy on Days 1, 8, and	<u>Primary</u> Progression-free survival (PFS)	No statistically significant change of PFS and OS was noted in patients receiving CX-01. Comparing Day 1 and Day 15 platelet counts in patients receiving gemcitabine + *nab*-paclitaxel with or without CX-01; a statistically significant increase was observed favoring CX-01 treatment. Among the 35 patients in this study treated with CX-01, 3 serious adverse events (pulmonary embolus, type II diabetes, and Grade 2 peripheral edema) were reported. The thromboembolic events were considered to be related to Trousseau's syndrome and underlying

Study Number	Phase	Indication	Number of Patients	Study Drug and Dose	Study Endpoints	Study Results
				15		disease.

Abbreviations: AE=adverse event, ALT=alanine aminotransferase, AML=acute myeloid leukemia, AST=aspartate aminotransferase, COPD=chronic obstruction pulmonary disease, CR=complete remission, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, hs-CRP=high sensitivity C-reactive protein, ITT=Intent-to-Treat, IV=intravenous, N=number, OS=overall survival, PFS=progression-free survival, PLE=protein losing enteropathy, PP=Per Protocol, SAE=serious adverse event. Note: Further details can be found in the Investigator's Brochure (63).

5. STUDY OBJECTIVES

This randomized, phase II study of CX-01 is designed to assess the effect of adding CX-01 at one of the two different dose levels to standard induction and consolidation therapy for newly diagnosed patients with AML.

5.1 Primary Objectives

The primary objectives are:

- To assess whether CX-01, administered at any or all studied dose levels in conjunction with standard induction therapy for AML increases the morphologic CR rate based on International Working Group (IWG) criteria

- To assess the safety and tolerability of CX-01, administered at two studied dose levels in conjunction with standard induction therapy for AML.

5.2 Secondary Objectives

The secondary efficacy objectives are:

To assess whether CX-01, administered at any or all studied dose levels in conjunction with standard induction and consolidation therapy for AML improves:

- Event-free survival (EFS)

- Leukemia-free survival (LFS)

- Overall survival (OS)

- Composite CR rate: incidence of CR + CRi, which is CR without recovery of neutrophils and/or platelets (ANC may be <1000 μL and/or platelet count <100,000/μL).

- Duration of morphologic CR

- 30-day mortality (in the induction cycle)

- 60-day mortality (in the induction cycle)

- 90-day mortality (in the induction cycle)

- Neutrophil recovery

- Platelet recovery.

6. INVESTIGATION PLAN

6.1 Overall Study Design and Plan Description

This is an exploratory phase II, open-label, randomized, multicenter, parallel group trial to determine whether there is evidence that the addition of either or both different dose levels of CX-01 to standard induction therapy (idarubicin + cytarabine) and consolidation therapy has an additive therapeutic effect in newly diagnosed AML patients when compared to patients receiving standard induction chemotherapy alone.

Approximately 75 patients will be randomized in a 1:1:1 ratio to one of the following treatment groups:

- **Group 1**: Idarubicin + Cytarabine, OR
- **Group 2**: Idarubicin + Cytarabine plus lower dose CX-01 (0.125 mg/kg/hour), OR
- **Group 3**: Idarubicin + Cytarabine plus higher dose CX-01 (0.25 mg/kg/hour)

Eligible patients who meet the inclusion criteria and do not meet any of the exclusion criteria and have provided informed consent will be enrolled in the study. Each patient will participate in the study for approximately 18 months from the time of informed consent through final study contact, or until they withdraw from the study or the study is terminated by the Sponsor.

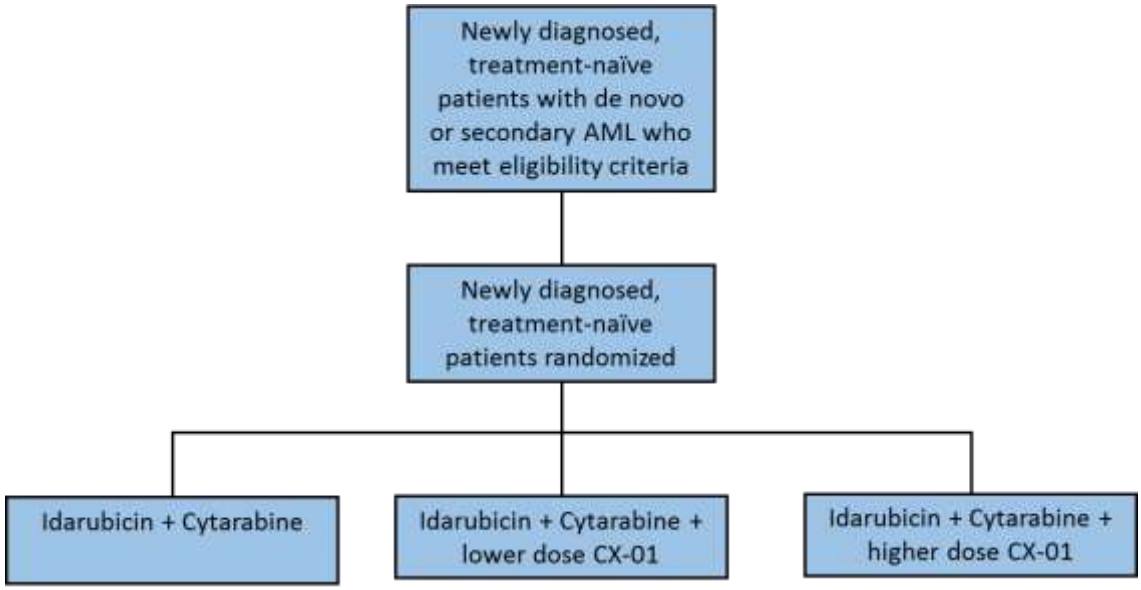
Overall survival data will be collected every 3 months until death or until the end of study by the investigational sites. The end of study will occur approximately 18 months after the last patient is randomized.

A Data and Safety Monitoring Committee (DSMC) will meet periodically to review the safety of the study (see Section 6.6.5). Details describing the DSMC process and procedures will be outlined in a separate DSMC Charter.

Adverse events (AEs) will be collected from time of informed consent and continue until 30 days after the last study treatment is administered. Longer follow-up and collection of AEs may be required for patients that do not have an absolute neutrophil count (ANC) recovery within 42 days (i.e., until the recovery or the reason for no recovery is diagnosed) after the last induction or consolidation cycle.

A flow diagram of the study design is shown in Figure 6—1.

Figure 6—1 Study Design



Abbreviations: AML=acute myeloid leukemia
Note: It is expected that approximately 90 patients will be screened to identify 75 patients for randomization.

6.2 Discussion of Study Design, Including the Choice of Control Groups

Approximately 75 patients will be randomized in a 1:1:1 ratio to receive standard induction and consolidation therapy with or without CX-01 at two different doses (lower and higher dose).

The anthracycline/cytarabine regimen using idarubicin (9-12 mg/m^2 daily) is considered a standard therapy for the majority of newly diagnosed patients with AML (64). Complete remissions are achieved in approximately 50% to 75% of patients (65). Dosing studies with continuous infusion cytarabine demonstrated that 100 mg/m^2 was as effective as 200 mg/m^2 (66,67).

The need for post remission therapy, following successful induction therapy, has been established in a number of clinical trials. It is presumed that most patients still have residual disease after the completion of induction chemotherapy (68). The standard treatment option includes consolidation therapy with intensive cytarabine-based chemotherapy regimens or allogeneic stem cell transplant.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Newly diagnosed, *de novo* or secondary, previously untreated AML
2. Age 60 or above
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix A)
4. Cardiac ejection fraction ≥45% (as determined by echocardiography or multi gated acquisition [MUGA] scan)
5. Adequate hepatic and renal function determined by the following laboratory values:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 x upper limit of normal (ULN)
    - Bilirubin <2.5 x ULN
    - Calculated creatinine clearance by Cockcroft Gault formula >30 mL/min (see Appendix C).
6. Able to provide informed consent and have signed an approved consent form that conforms to federal and institutional guidelines.

6.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patients with acute promyelocytic leukemia based on the presence of t(15;17)(q22;q12) (69) as determined by karyotyping, fluorescence in situ hybridization or polymerase chain reaction

2. Prior chemotherapy for AML (including investigational therapy); prior hydroxyurea to control WBC count and a single intrathecal administration of cytarabine for CNS prophylaxis is allowed

3. Prior intensive chemotherapy or stem cell transplantation for treatment of myelodysplastic syndrome (prior treatment with hypomethylating agents and lenalidomide are allowed)

4. Presence of central nervous system leukemia

5. Presence of significant active infection that is not controlled in the opinion of the Investigator

6. Presence of significant active bleeding

7. History of severe congestive heart failure or other cardiac disease that contraindicates the use of anthracyclines, including idarubicin

8. Pre-existing liver disease (such as CHILD-Pugh Class B or C liver disease; see Appendix D)

9. Renal insufficiency which might adversely affect schedule and dose of therapy with cytarabine as well as management of tumor lysis syndrome.

10. History of drug addiction within the last 6 months

11. Known history of positive Hepatitis B surface antigens

12. Known history of positive test for Human Immunodeficiency Virus antibodies

13. Psychiatric or neurologic conditions that could compromise patient safety or compliance, or interfere with the ability to give proper informed consent

14. History of other active malignant disease within the past 3 years, other than cured basal cell carcinoma of the skin, cured in situ carcinoma of the cervix, or localized prostate cancer that has received definitive therapy. Such prostate cancer patients who are receiving hormonal therapy are eligible

15. Patients receiving any form of anticoagulant therapy (heparin flushes for IV

catheter permitted)

16. Presence of a known bleeding disorder or coagulation abnormality (including but not limited to aPTT >40 seconds) or any condition that requires maintenance of platelet counts at 50,000/μL or higher

17. Pregnant or breast feeding patients

18. Patients of childbearing potential not using adequate contraception.

6.3.3 Withdrawal and Discontinuation of Patients

Patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a patient from treatment:

- The patient was erroneously included in the study (i.e. was found to be ineligible)
- The patient experiences an intolerable or unacceptable AE
- The patient is unable to comply with the requirements of the protocol
- The patient participates in another investigational study without the prior written authorization of the Sponsor or its designee
- The patient's participation in the study presents a significant safety concern.

Patients who experience Grade 4 increases in AST, ALT or bilirubin (e.g., increase in AST or ALT >20 x ULN; increase in total bilirubin to >10 x ULN) will be discontinued from the study, if the Investigator judges that the laboratory abnormalities are potentially related to study treatment. Patients discontinued for this reason will not be re-challenged and will be followed until resolution of abnormal liver function tests.

Patients who are discontinued from study due to an AE will be closely monitored until the resolution or stabilization of the AE.

Patients who received at least one dose of study drug and who are discontinued from treatment, but not withdrawn from the study, will be asked to complete all evaluations for early termination (Early Termination/End of Study Visit).

Patients who discontinue from the study will not be replaced.

6.4 TREATMENT OF PATIENTS

6.4.1 Treatments Administered

For induction therapy, all patients will receive standard idarubicin + cytarabine chemotherapy. Patients randomized to Groups 2 and 3 will also receive CX-01. CX-01 will be continually infused while idarubicin will be administered per institutional standard.

Group 1: Idarubicin + Cytarabine

- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7.

Group 2: Idarubicin + Cytarabine + plus lower dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1 only, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-7
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7.

Group 3: Idarubicin + Cytarabine + plus higher dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1 only, 30 minutes after completion of administration of the first dose of idarubicin, followed by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-7
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-7.

Re-induction Therapy

A bone marrow aspirate and biopsy will be performed between Days 14-21 of the induction cycle. If bone marrow shows leukemia-free state, i.e. less than 5% blasts in a aspirate sample, no further chemotherapy will be given until recovery of blood counts. If the bone marrow shows more than 5% blasts, a re-induction cycle may be given as outlined above. If the Days 14-21 marrow is indeterminate e.g., if there is a question of residual leukemia, a bone marrow aspirate may be repeated 7 days later for confirmation. Re-induction will be given with the same assigned regimen ("7 + 3" ± CX-01) as

administered during the first induction cycle as outlined above.

If in the Investigator's opinion, the patient is not fit to receive full re-induction cycle of "7 + 3" ± CX-01 at the Investigator's discretion the patient may receive "5 + 2" ± CX-01 which is 5 days of cytarabine and 2 days of idarubicin as outlined below:

Group 1: Idarubicin + Cytarabine

- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Group 2: Idarubicin + Cytarabine + plus lower dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of administration of the first dose of idarubicin followed by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Group 3: Idarubicin + Cytarabine + plus higher dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of administration of the first dose of idarubicin followed by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5
- Idarubicin 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1 and 2
- Cytarabine 100 mg/m^2/day by continuous 24-hour IV infusion on Days 1-5.

Consolidation Therapy

Evaluation for remission will take place at the time of count recovery, or, if no count recovery is achieved, at approximately Day 35 if the patient received one induction course or approximately Day 49 if the patient received re-induction course. Count recovery is defined as ANC >1,000/µL and platelet count of >100,000/µL. Remission will be defined according to IWG criteria (Appendix A). For patients with documented CR, confirmatory bone marrow aspirate slides will be submitted to the Sponsor or designee.

Patients in remission at the end of induction may proceed to consolidation therapy on study, depending upon factors including, but not limited to, European Leukemia Net (ELN) (70) genetic risk and co-existing conditions.

Patients who are not in CR at the end of re-induction will be taken off study and will complete Early Termination Visit as per Table 6—1.

Patients who could benefit from and are eligible to undergo stem cell transplantation will go off the study at any time when transplant is feasible.

Patients will receive up to two cycles of consolidation therapy on study, per NCCN guidelines, depending upon factors including, but not limited to, ELN genetic risk and co-existing conditions. A cycle of consolidation therapy is defined as the time from initiation of chemotherapy on Day 1 until count recovery.

Patients may start consolidation therapy anywhere from 4 to 8 weeks after the start of induction therapy based on treating Investigator judgment. Consolidation will begin no sooner than 28 days from the start of induction therapy.

Subsequent consolidation cycles may begin anywhere from 4 to 8 weeks after the start of the last cycle of consolidation based on treating Investigator judgment.

Patients will receive consolidation therapy in the same treatment group as assigned at randomization, as follows:

Group 1: Cytarabine

- Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.

Group 2: Cytarabine + lower dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of the first 3-hour infusion of cytarabine, followed immediately by CX-01 0.125 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5 for a total of 120 hours of continuous CX-01 infusion

- Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.

Group 3: Cytarabine + higher dose CX-01

- CX-01 given as a 4 mg/kg initial bolus on Day 1, 30 minutes after completion of the first 3-hour infusion of cytarabine, followed immediately by CX-01 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5 for a total of 120 hours of continuous CX-01 infusion

- Cytarabine 1.0 gram/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.

6.4.1.1 Transfusions

- Red blood cell (RBC) transfusion will be administered according to institutional guidelines

- Platelet transfusions will also be given at the discretion of the treating Investigator based on clinical characteristics and patient need.

6.4.1.2 Dosing and Method of Administration

All chemotherapy and CX-01 doses will be calculated based on actual body weight at the beginning of each cycle of induction or consolidation therapy.

Chemotherapy will be administered through a central venous catheter, such as a peripherally inserted central catheter, with two or three independent ports. This catheter may also be used for administration of blood products, IV medications and IV fluids.

CX-01 bolus and continuous infusions may be administered in the same arm through a peripheral IV line; however, must be separate from the central line or port used for chemotherapy.

6.4.1.3 Preparation of CX-01 Infusion

The Investigator and pharmacist at the investigational site will ensure Good Pharmacy Practices are followed during the preparation of the CX-01 IV solution. The volumes and CX-01 concentration in the final CX-01 IV solutions must be verified to be correct based on the patient's actual body weight measured at the beginning of the cycle.

6.4.1.4 Preparation of CX-01 Intravenous Bolus Dose

The pharmacist will prepare the IV bolus resulting from the 4 mg/kg dose calculation with the amount of CX-01 from the appropriate number of 10 mL vials. Each 1 mL solution contains 50 mg CX-01 and must be further diluted in 0.9% sodium chloride. This calculated volume per patient (based on weight) will be added to 30 mL of 0.9% sodium chloride solution and the total volume administered IV over 5 minutes.

6.4.1.5 Preparation of CX-01 Continuous Infusion Dose

The pharmacist will prepare each study treatment solution, adding the calculated amounts of CX-01 and 0.9% sodium chloride to an empty, sterile infusion bag. An IV infusion line will then be attached to the infusion bag, and the infusion set purged with the CX-01 solution. A Luer lock (or similar) will then be placed at the end of the set. As CX-01 doses are weight based, the amount of CX-01 from the vials and saline solution will both vary by patient's weight. Each 1 mL solution contains 50 mg CX-01.

For each continuous infusion bag, an appropriate volume and concentration of CX-01 solution will be prepared such that the patient receives a continuous infusion at the dose

of CX-01 assigned at randomization, 0.125 or 0.25 mg/kg/hour. The final volume of the CX-01 infusion will be 500 to 1000 mL/24 hours. The infusion bags will be prepared at a calculated CX-01 concentration based on the patient's actual body weight.

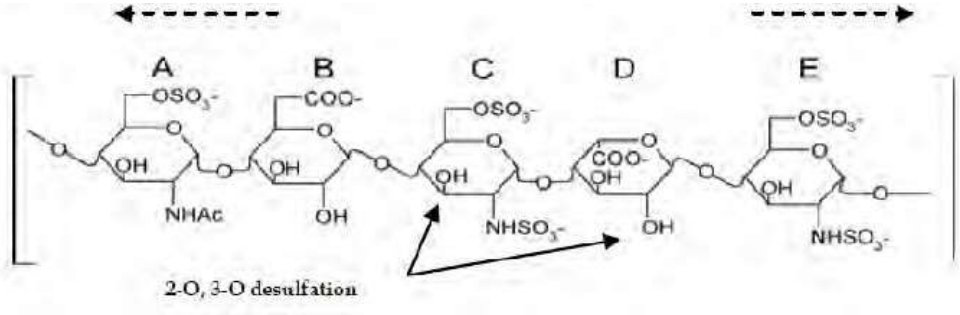
Based upon current stability testing data, CX-01 infusion solutions will expire at room temperature 72 hours after preparation and should be stored in a refrigerator (2 to 8ºC) until used.

If the IV infusion is interrupted for any reason, the time of infusion stop will be recorded, along with the reason. The IV infusion will be restarted as soon as possible, and the restart time recorded. The planned cycle days of treatment administration will not be altered, nor will the concentration of the CX-01 solution be adjusted, to compensate for an interrupted CX-01 infusion.

6.4.2 Investigational Product

CX-01 (2-O, 3-O desulfated heparin [ODSH]) is an off-white to pinkish amorphous powder. CX-01 is a low anticoagulant, anti-inflammatory UFH derivative produced for human use compliant with current Good Manufacturing Practices (cGMP). The structural formula for the basic repeating unit that comprises CX-01 is provided in Figure 6—2.

Figure 6—2 Structure of CX-01



Further details are provided in the IB (63).

6.4.2.1 Packaging and Labeling

Idarubicin and cytarabine will be obtained from commercial sources. These treatments will be prepared by the investigational site pharmacy using standard institutional procedures according to the respective package insert for each agent.

Adequate supplies of the study drug, CX-01, will be provided to each investigational site. The study drug (CX-01) was manufactured under cGMP and will be supplied by Sponsor and packaged in 10 mL sterile, single -use glass vials. The 10 mL vial contains 500 mg total CX-01 (50 mg per mL).

Each vial will be labeled in English and in accordance with United States (US)

requirements since all investigational sites participating in the study will be in US. Label text will be approved according to the Sponsor's agreed procedures. The lot numbers and expiration dates of the batches of CX-01 vials used in this study will be printed on the vial labels.

For all vials, a system in accordance with cGMP will be used; ensuring each dose of study drug can be traced back to the respective bulk ware of the ingredients. A complete record of batch numbers and expiry dates of all study drug and labels will be maintained in the Sponsor's study file.

6.4.2.2 Storage and Stability

The study medication must be stored in a secure limited access area according to local regulations. CX-01 vials should be stored at room temperature, preferably between 5ºC and 25ºC (41 F to 77ºF).

Long term stability testing for active pharmaceutical ingredient (API) and final product (CX-01 vials) was conducted in compliance with FDA requirements. Results from these stability studies indicate that CX-01 API and CX-01product are stable for at least 48 months when stored at room temperature. The API and final product studies are being conducted with current production material to confirm prior results and extend the study period to 72 months. A stability study of CX-01 in normal saline diluted for bolus dose concentration and continuous infusion concentration (in polyethylene bags) has confirmed stability of the drug product for at least 72 hours (the maximum period tested) at two concentration levels and at two temperature conditions (2ºC to 8ºC and room temperature). This testing covers all the ranges for CX-01 concentration/dilution required when dosing for clinical trials.

Since CX-01 vials are photo-stable, there is no need to protect from direct or indirect light.

6.4.2.3 Study Drug Accountability, Reconciliation, and Return

Upon completion and termination of the study, all unused and/or partially used study drug must be returned to the Sponsor, or other authorized party if not authorized by the Sponsor to be destroyed at the site.

All study drugs returned to the Sponsor or other authorized party must be accompanied by the appropriate documentation and be clearly identified. Study drug may only be returned after drug accountability is completed. Returned supplies should be in their original containers (vials that have clinical labels attached). Empty vials should not be returned to the Sponsor. Empty vials may not be destroyed until drug accountability is completed. It is the Investigator's responsibility to arrange disposal of all empty vials according to institutional regulations. The return or destruction of unused study drug should be arranged by the site Monitor.

6.4.2.4 Study Drug Handling and Disposal

The Sponsor will be responsible for assuring that the quality of the study drug is adequate for the duration of the study. It is the responsibility of the Investigator or designee to ensure that the study drug is only dispensed to the patient. The study drug must be dispensed only from official study sites by authorized personnel according to local regulations. The Investigator or designee must maintain accurate records of the study drug receipt, dispensing information, and disposition.

If study drug is to be destroyed at the site, it is the Investigator or designee's responsibility to ensure that arrangements have been made for the disposal, drug accountability has been completed by the site Monitor, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented and provided to the Sponsor or designee.

6.4.3 Method of Assigning Patients to CX-01

6.4.3.1 Patient Identification

Each newly enrolled patient will be assigned a unique patient identification number using an Interactive Web/Voice Response System (IxRS). Patients will be randomized across all sites. Patients who discontinue from the study will not be replaced.

6.4.4 Selection of Doses in the Study

6.4.4.1 Selection of Dose

The selection of CX-01 dose for study in AML has been based upon the dual requirements to have sufficient drug administered to have potential activity but without clinically significant anticoagulation. The study dose chosen (4 mg/kg bolus followed by 0.125 or 0.25 mg/kg/hour for 5 or 7 days) fulfills both of these criteria. In addition, all doses are expected to result in serum levels of CX-01 which are significantly higher than the IC90 identified in preclinical studies for inhibition of CXCL12-CXCR4 interaction.

In a pilot study of CX-01 conducted on 12 patients with newly diagnosed AML, the addition of CX-01 to the traditional "7 + 3" regimen of cytarabine and idarubicin resulted in 11 of 12 patients achieving complete bone marrow remission after the first cycle (92%). It was hypothesized that the increased rate of first cycle induction of remission was from blockade by CX-01 of CXCL12 (SDF-1)/CXCR4-mediated homing of LSC in the marrow niche where they are protected from chemotherapy. The dose and regimen of CX-01 in that trial were well tolerated without associated serious AEs (SAEs). Mean levels of aPTT remained largely in the mid-30 second range.

In a prior study of continually infused CX-01 in patients with metastatic pancreatic cancer (Study PGX-ODSH-2011-PC), CX-01 was administered as an IV bolus loading dose of 4 mg/kg, followed by a continuous infusion of 0.375 mg/kg/hour for 5 days. This

dose was well tolerated and free from major AEs. However, measurement of aPTT in these patients demonstrated that aPTT was increased into the 40 to 45 second range in a limited number of patients. This is a range that is not overtly anticoagulant, but higher than the therapeutic range of aPTT (31.5 to 36 seconds).

Therefore, the chosen dose (4 mg/kg bolus followed by 0.125 or 0.25 mg/kg/hour) represents a rational balance between effective dosing and safety in seriously ill patients with AML.

6.4.4.2 Dose Modifications

No dose modification for cytarabine or idarubicin during induction will be allowed. However, dose reduction of cytarabine during consolidation is permitted according to institutional guidelines, or if in the Investigator's opinion the patient cannot tolerate a higher dose.

CX-01 Dose Modifications

- CX-01 will be temporarily discontinued in patients who develop aPTT above 45 seconds during continuous infusion of CX-01 and at least 8 hours after the bolus dose of CX-01, until the aPTT is <35 seconds. CX-01 will then be resumed at a 50% dose reduction. If the aPTT rises above 45 seconds at the reduced dose, CX-01 will be permanently discontinued. If aPTT at the 50% reduced dose is <35 seconds, 4 hours or more after dose reduction, the dose can be escalated by 25%. If the aPTT after dose escalation again rises above 45 seconds at the reduced dose, the CX-01 will be temporarily discontinued until the aPTT is <35 seconds, and then resumed at the previous 50% dose reduction.

- Abnormal liver function:

    - If Grade 1 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT from ULN to 3.0 x ULN; increase in total bilirubin from ULN to 1.5 x ULN), the frequency of liver function testing will be increased, if the Investigator judges that the laboratory abnormalities are potentially related to study treatment. No reduction of dose is required

    - If Grade 2 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to >3.0 to 5 x ULN; increase in total bilirubin from >1.5 to 3 x ULN), the frequency of liver function testing will be increased to ≥once a week, if the Investigator judges that the laboratory abnormalities are potentially related to study treatment. No reduction of dose is required

    - If Grade 3 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to >5.0 to 20 x ULN; increase in total bilirubin from >3.0 to 10 x ULN) and if the Investigator judges that the laboratory abnormalities are potentially related to study treatment, study drug must be stopped. Frequent laboratory evaluations (more than once weekly) will be

conducted until liver function tests return to Grade 1 or baseline value. Study treatment will be resumed after liver function tests return to Grade 1 or baseline value provided administration of chemotherapy is in progress. If resumption of study treatment is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin liver function will be monitored at least daily during CX-01 infusion

- If Grade 4 increases in AST, ALT, or bilirubin occur (e.g., increase in AST or ALT to >20 x ULN; increase in total bilirubin to >10 x ULN) and if the Investigator judges that the laboratory abnormalities are potentially related to study treatment, the patient must discontinue study treatment immediately and will not be re-challenged. The patient will be followed until resolution of abnormal liver function tests.

- Renal function:

  If the calculated creatinine clearance drops below 30 mL/min/1.73m^2 prior to or during dosing with CX-01, the dose of CX-01 will be held until the creatinine clearance rises above 30 mL/min/1.73m^2.

- For any other Grade 3 or 4 toxicities that appear to be related to CX-01 during either the induction or consolidation cycles, CX-01 will be interrupted until the AE resolves to Grade 1 or less, and then resumed at 0.125 mg/kg/hour provided administration of chemotherapy is in progress. If CX-01 is interrupted for greater than 72 hours, the patient will be discontinued from treatment. If the AE recurs at a level of Grade 3 or higher, the CX-01 will be discontinued.

This study will utilize the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 for AE and SAE reporting. A copy of the CTCAE Version 4.03 can be downloaded: (http://safetyprofiler ctep.nci.nih.gov/CTC/CTC.aspx).

6.4.5 Prior and Concomitant Medications

The Investigator must record the use of all concomitant medications taken during 30 days prior to signing informed consent and for the duration of the study until the Safety Follow-Up Visit, both prescribed and over-the-counter, in the source documents and electronic case report form (eCRF). Patients should be discouraged from starting any new medication, both prescribed and over-the-counter, without consulting the Investigator unless the new medication is required for emergency.

6.4.5.1 Permitted Concomitant Medications

Refer to Section 6.4.1.1 for transfusion parameters. Treatment for disease-related symptoms and drug-related toxicities are expected as standard of care and should be recorded in the patient's medical record and eCRF.

The use of myelopoietic growth factors (G-CSF and GM-CSF) is allowed, consistent with the Investigator's clinical judgment and institutional guidelines.

6.4.5.2 Prohibited Concomitant Medications

Patients are not permitted to take those medications specified in the exclusion criteria (Section 6.3.2).

The following medications are prohibited:

- Any anticoagulation therapy (with the exception of heparin flushes). CX-01 IV bolus doses may cause a slight transient increase of aPTT (to approximately 60 seconds) for less than 1 hour, while the continuous IV infusion at the doses to be used in this study, based upon previous studies, will raise the aPTT to the ULN or to a level (approximately 35 to 45 seconds) that is not of clinical significance. CX-01 may, however, potentiate the anticoagulation effect of UFH, LMWH or anticoagulants if administered concomitantly. Therefore, concomitant administration of CX-01 with other anticoagulants will not be permitted in patients participating in this study other than as heparin flushed to maintain IV line patency.

- Any investigational therapeutic agents.

6.4.6 Treatment Compliance

Since all treatments are administered at the clinical site by site personnel, the Investigator or designee must maintain accurate records of all study treatments, including dates of study drug receipt; quantities received and dispensed, and lot numbers. In addition, the study treatment must be noted in the patient's medical records and eCRF, with the date and time of administration and dose of each study treatment.

6.5 Study Procedures

6.5.1 Schedule of Study Procedures

Table 6—1 presents induction/re-induction cycles and Table 6—2 presents' consolidation cycles.

Table 6—1 Induction/Re-induction Cycle Schedule of Study Procedures

Examination	Screen Visit D -28 – 1	D1	D2	D3	D4	D5	D6	D7	D 8-13	D 14-21	At count recovery & Weekly from D21 until count recovery or D60[15]	Early Term Visit	Safety FU visit (30 days after last dose of treatment)	Long Term FU contact (every 3 months up to death, or EoS) [16]
Informed consent[1]	X													
Demographic and medical history	X													
Eligibility criteria	X	X												
Randomization		X												
Idarubicin [2]		X	X	X										
Cytarabine[3]		X	X	X	X	X	X	X						
CX-01 Bolus[4]		X												
CX-01[5] continuous infusion		X	X	X	X	X	X	X						
ECOG status	X													
Vital signs (BP, heart rate, height and weight)[6]	X													
Physical exam	X													
12-lead ECG	X							X						
Echocardiography or MUGA scan	X													
Hematology[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-factor Xa[8,9]	X	X	X	X	X	X	X	X	X[9]			X		
PT/INR, aPTT[8,10]	X	X	X	X	X	X	X	X	X[10]	X	X	X	X	

Table 6—1 Induction/Re-induction Cycle Schedule of Study Procedures

Examination	Screen Visit D -28 – 1	D1	D2	D3	D4	D5	D6	D7	D 8-13	D 14-21	At count recovery & Weekly from D21 until count recovery or D60[15]	Early Term Visit	Safety FU visit (30 days after last dose of treatment)	Long Term FU contact (every 3 months up to death, or EoS) [16]
Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK sampling[12]				X		X								
AE Assessment	Continuously →													
Previous medications	X													
Concomitant medications	continuously →													
Fibrinogen, D-dimer	X										X	X	X	
Serum or urine pregnancy test[13]	X												X	
Bone marrow aspirate/ Biopsy[14]	X[14]									X[14]	X[14]			
Relapse and survival data														X

Abbreviations: AE=adverse event, ALT=alanine aminotransferase, ANC=absolute neutrophil count, anti-Xa=anti-factor 10a, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BP=blood pressure, BUN=blood urea nitrogen, CBC=complete blood count, CX-01=2-O, 3-O desulfated heparin, D=day, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EoS=end of study, FU=follow-up, INR=international normalized ratio, IV=intravenous, LDH=lactate dehydrogenase, MUGA=multi gated acquisition, OS=overall survival, PK=pharmacokinetics, PT=prothrombin time, Term=termination.

1. Informed consent must be obtained before any study-related procedures are conducted.

2. Idarubicin administered at a dose of 12 mg/m^2/day by slow (10 to 30 minutes) IV injection/infusion daily on Days 1, 2, and 3.
3. Cytarabine administered at a dose of 100 mg/m^2/day as a continuous 24-hour IV infusion on Days 1-7. Patients who do not achieve leukemia-free state (<5% bone marrow blasts) on bone marrow aspirate performed between Days 14-21 may receive a re-induction cycle with the same regimen ("7 + 3" ± CX-01). If in the Investigator's opinion, the patient is not fit to receive full re-induction cycle of "7 + 3" ± CX-01, at the Investigator's discretion the patient may receive "5 + 2" ± CX-01 which is 5 days of cytarabine (Days 1-5) and 2 days of idarubicin (Days 1 and 2).
4. CX-01 administered at a dose of 4 mg/kg as an initial bolus on Day 1 only, 30 minutes after completion of administration of the first dose of idarubicin.
5. CX-01 administered at a dose of 0.125 or 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-7.
6. Height obtained at Screening only. Actual body weight will be measured at the beginning of each cycle to calculate treatment doses.
7. Hematology **must** include the following: hemoglobin, ANC, and platelets. All other hematology assessments should be performed only if standard of care and/or clinically indicated. Hematology samples will be collected daily until discharge and weekly thereafter until recovery.
8. Note: blood samples for PT/INR, aPTT and anti-Xa levels will be collected 12 hours after the bolus dose of CX-01.
9. Anti-Xa samples will be collected only on Days 1-8.
10. PT/aPTT will be collected daily on Days 1-8, and on Day 9, Day 11, and Day 13.
11. Chemistry (and comprehensive metabolic panel) includes BUN, serum creatinine, total bilirubin, ALT, AST, and alkaline phosphatase. Samples will be collected daily until discharge.
12. At selected sites, blood samples for steady-state PK analysis will be collected during the induction cycle from the first six randomized patients assigned to CX-01 on Days 3 and 5 at a single time point.
13. For females of childbearing potential only. All female patients will have a urine pregnancy test at Screening; positive urine tests must be confirmed by a serum pregnancy test.
14. Bone marrow aspirates and/or biopsies are not performed weekly. If the patient's peripheral blood is negative for persistent AML: a bone marrow aspirate and/or biopsy will be performed (once) between Days 14-21 to determine the need for re-induction. Bone marrow biopsy may be necessary if sufficient spicules are not available on aspirate. Bone marrow aspirate at baseline and follow-up should include analysis by flow cytometry and cytogenetic analysis. Bone marrow (or peripheral blood if bone marrow is unavailable) should be sent to the institution's local cytogenetic laboratory for analysis. For patients with documented CR, confirmatory bone marrow aspirate slides will be submitted to the Sponsor or designee. If count recovery has not occurred by Day 42, a bone marrow aspirate/biopsy will be performed to evaluate disease status, unless presence of persistent AML in peripheral blood.
15. Count recovery is defined as ANC of >1000/μL and a platelet count >100,000/μL.
16. During long term follow-up, relapse and survival data will be collected every 3 months until death or until the end of study. The end of study will occur approximately 18 months after the last patient is randomized.

Table 6—2 Consolidation Cycle Schedule of Study Procedures

Examination	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**Weekly from D6 until count recovery[8]**
Hematology[1]	X	X	X	X	X	X
PT/INR, aPTT, and anti-Xa[2]	X	X	X	X	X	
Chemistry[3]	X	X	X	X	X	X
Vital signs (BP, heart rate, height and weight)[4]	X					
Cytarabine[5]	X		X		X	
CX-01 Bolus[6]	X					
CX-01[7] continuous infusion	X	X	X	X	X	
Concomitant medications	continuously →					
Adverse events	continuously →					
Bone marrow aspirate/ Biopsy						X[9]

Abbreviations: aPTT=activated partial thromboplastin time, anti-Xa=anti-factor 10a, BP=blood pressure; CBC=complete blood count, D=day, INR=international normalized ratio, PT=prothrombin time.

1. Hematology **must** include the following: hemoglobin, ANC, and platelets. All other hematology assessments should be performed only if standard of care and/or clinically indicated. Hematology samples will be collected daily until discharge and weekly thereafter until recovery.

2. PT/aPTT and anti-Xa blood samples will be collected 12 hours after the bolus dose of CX-01.
3. Chemistry (and comprehensive metabolic panel) will be collected daily until discharge.
4. Actual body weight will be measured at the beginning of each cycle to calculate treatment doses.
5. Cytarabine administered at a dose of 1.0 g/m^2 over 3 hours, every 12 hours on Days 1, 3, and 5.
6. CX-01 administered at a dose of 4 mg/kg as an initial bolus on Day 1, 30 minutes after completion of the first 3-hour infusion of cytarabine, followed immediately by a continuous CX-01 24-hour IV infusion.
7. CX-01 administered at a dose of 0.125 or 0.25 mg/kg/hour as a continuous 24-hour IV infusion on Days 1-5 for a total of 120 hours of continuous CX-01 infusion.
8. Count recovery is defined as ANC of >1000/µL and a platelet count >100,000/µL.
9. Bone marrow aspirate/biopsy is not done weekly. If the patient's peripheral blood is negative for persistent AML and count recovery has not occurred by Day 42 (of Consolidation cycle), a bone marrow aspirate/biopsy will be done to evaluate disease status.

6.5.2 Screening Procedures

Eligibility will be assessed at the Screening Visit. Informed consent will be obtained at the Screening Visit, prior to performing any study-related procedures. All inclusion criteria must be met and all exclusion criteria must be absent for the patient to qualify for enrollment in the study. The Screening period may last no more than 28 days before the patient is randomized in the study.

The following will be conducted and all results will be documented during Screening:

- Informed consent
- Demographics and medical history
- Eligibility criteria assessment according to inclusion/exclusion criteria
- ECOG performance status
- Vital signs (including heart rate, blood pressure [BP], height, and weight)
- Physical exam
- 12-lead electrocardiogram (ECG)
- Echocardiography or MUGA scan for cardiac ejection fraction
- Clinical laboratory assessments (serum chemistry, hematology, and coagulation testing). All Screening laboratory tests will be performed locally
- Fibrinogen, D-dimer
- Assessment of AEs
- Assessment of previous and concomitant medications (including anti-cancer medications). All concomitant medications and medications taken within 30 days prior to informed consent must be documented
- Urine pregnancy test will be performed for all female patients of childbearing potential; positive urine tests will be confirmed by a serum pregnancy test
- Bone marrow aspirate/biopsy.

6.5.3 Randomization

Randomization will occur after eligibility is confirmed for consenting study participants. Study drug will be administered following randomization.

6.5.4 Treatment Procedures

Induction/re-induction cycle

- Administration of standard chemotherapy; idarubicin on Days 1-3 and cytarabine on Days 1-7
- Administration of CX-01 as an initial bolus on Day 1 only
- Administration of CX-01 as a continuous infusion on Days 1-7

  (Note: if a patient is not fit to receive the full re-induction cycle of "7 + 3" ± CX-01, at the Investigator's discretion the patient may receive "5 + 2" ± CX-01 which is 5 days of cytarabine [Days 1-5] and 2 days of idarubicin [Days 1 and 2]).
- 12-lead ECG on Day 7
- Clinical laboratory assessments
- Assessment of AEs
- Assessment of concomitant medications
- PK sampling on Days 3 and 5 (performed at selected sites and collected during the induction cycle from the first six randomized patients assigned to CX-01).

Consolidation cycle

- Administration of cytarabine on Days 1, 3, and 5
- Administration of CX-01 as an initial bolus on Day 1
- Administration of CX-01 as a continuous infusion on Days 1-5
- Clinical laboratory assessments
- Assessment of AEs
- Assessment of concomitant medications.

6.5.5 Safety Follow-Up Visit

Patients will complete a Safety Follow-Up Visit approximately 30 days after completion of the last induction or consolidation cycle. See Table 6—1 for clinical assessments performed at this visit. Longer follow-up may be required for patients who do not have an ANC recovery by Day 42 (that is, until the recovery or until a reason for no recovery is diagnosed) after the last induction or consolidation cycle.

6.5.6 Early Term Visit

In case of early termination, the following will be conducted (see Table 6—1 for details) and all results will be documented:

- Hematology
- PT/INR, aPTT, and anti-factor Xa
- Chemistry
- AE Assessment
- Concomitant medications
- Fibrinogen, D dimer

6.5.7 Long Term Follow-Up

After Safety Follow-Up Visit, the relapse and survival data will be collected every 3 months.

Each subject will participate in the long term follow-up for approximately 18 months from the time of informed consent until death or until the end of the study (for the definition of end of study, see Section 6.1).

Investigational sites are expected to make every effort to obtain long term follow-up data. This level of diligence is necessary to ascertain the patient's health status, and thus avoid lost to follow-up status for efficacy assessments. Follow-up may require:

- Permission for study personnel to contact an alternative person (e.g., family, spouse, partner, legal representative, or physician) even if only by telephone
- Permission for study personnel to access and review the patient's medical information from alternative resources (e.g., doctors notes, hospital records)

Attempts to contact patients must be documented in the patient's source documents and in the eCRF. The source documents for OS may be sent remotely to the site Clinical Research Associate for review and verification (ensuring patient identifiers are redacted except for study number and initials).

6.6 EFFICACY AND SAFETY VARIABLES

6.6.1 Appropriateness of Measurements

The safety and efficacy measurements used in the evaluation of the study endpoints are widely used and recognized as reliable, accurate, and conform to standard of care.

Response will be evaluated according to IWG criteria (see Appendix A), which has been published and validated and is appropriate for use in this study.

6.6.2 Efficacy Assessments

6.6.2.1 Primary Efficacy Assessment

The primary endpoint is the rate of patients in each treatment group achieving morphological CR based on IWG criteria during the induction and re-induction phases of the treatment. Morphologic CR is defined as ANC >1000/μL, platelet count >100,000/μL, <5% blasts in an bone marrow aspirate sample, no blasts with Auer rods, and no evidence of extramedullary disease (see Appendix A).

6.6.2.2 Secondary Efficacy Assessments

6.6.2.2.1 Event-Free Survival

Event-free survival is measured from the date of randomization until treatment failure (e.g., failure to achieve composite complete morphological remission during the induction or re-induction phase of the study lasting up to 60 days, relapse from CR, or death from any cause, whichever occurs first).

6.6.2.2.2 Leukemia-Free Survival

Leukemia-free survival is only assessed in patients who achieve composite CR and is measured from the date of randomization until disease relapse or patient death from any cause, whichever occurs first.

6.6.2.2.3 Overall Survival

Overall survival is measured from the date of randomization until death from any cause.

6.6.2.2.4 Composite Complete Remission Rate

Complete remission rate includes CR, CR without recovery of platelets (CRp) and CRi as defined by IWG criteria (Appendix A) during the induction and re-induction phases of treatment.

6.6.2.2.5 Duration of Morphologic Complete Remission

Duration of morphologic complete response is measured from the achievement of CR to detection of relapse.

6.6.2.2.6 30-Day, 60-Day and 90-Day Mortality

Thirty-day, 60-day, and 90-day mortality are the rate of death during 30 days, 60 days, and 90 days, respectively, from the first day of induction treatment.

6.6.2.2.7 Neutrophil and Platelet Recovery

Time to neutrophil recovery is measured from the date of randomization until ANC recovers to >1000/μL.

Time to transfusion-independent platelet recovery is measured from the date of randomization until the first day that the platelet count recovers to >100,000/μL (provided it is not as a consequence of platelet transfusion and provided platelets are then maintained at >100,000/μL for the five subsequent days without platelet transfusion).

6.6.3 Safety Assessments

Key safety endpoints will be assessed by review of summaries of AEs which will include only treatment-emergent AEs (TEAEs), unless otherwise stated. Adverse events will be categorized by System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 14.1), and will be graded according to NCI-CTCAE version 4.03.

6.6.3.1 Adverse Events

Adverse events will be monitored throughout the study. Adverse events will be collected from the time of informed consent and continue until 30 days after the last study treatment is administered. Longer follow-up and collection of AEs may be required for patients who do not have an ANC recovery by Day 42 (i.e., until the recovery or until a reason for no recovery is diagnosed) after the last induction or consolidation cycle.

For the purpose of this study, the terms toxicity and AE are used interchangeably.

6.6.3.2 Definitions

6.6.3.2.1 Definition of an Adverse Event

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or casually associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs the term “condition” may include abnormal symptoms, diseases, laboratory, or vital sign findings.

- Conditions that started before signing of ICF and for which no symptoms or treatment are present until signing of ICF are recorded as medical history (e.g.,

seasonal allergy without acute complaints)

- Conditions that started before signing of ICF and for which symptoms or treatment are present after signing of ICF, at unchanged frequency and/or intensity, are recorded as medical history (e.g., allergic pollinosis)

- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

Abnormal laboratory and other abnormal investigational findings (i.e., physical exam) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are otherwise considered clinically relevant by the Investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In a case of fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Medical conditions/diseases present before starting study drug are considered to be an AE only if they worsen after starting study drug and are clearly not related to cytarabine and/or idarubicin toxicities, or to AML that is not yet in remission. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs and symptoms, are considered clinically significant, or require therapy.

Information about all AEs, whether volunteered by the patient, discovered by the Investigator or designee questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded, as appropriate.

As far as possible, each AE should be evaluated to determine:

- The severity grade based on NCI-CTCAE version 4.03 (Grade 1 to 5)

- The relationship to the study drug(s) (see Section 6.6.3.2.6). A relationship between the AE and the underlying AML, the dose-intensive chemotherapy, and CX-01 treatment, will be assessed

- The duration (start and end dates or continuing at final contact)

- Action taken (no action taken, study drug dosage adjusted/temporarily interrupted, study drug permanently discontinued due to this AE, concomitant medication taken, non-drug therapy given, hospitalization/prolonged hospitalization, see Section 6.6.3.2.7)

- Whether it constitutes an SAE.

All AEs will be treated appropriately. Such treatment may include changes in study drug

treatment as listed in the dose modification section of the protocol (Section 6.4.4.2). Adverse events will be followed until resolution or stabilization of the event, completion of the patient's participation, or study termination, or the Investigator or designee and Sponsor agree that follow-up is no longer necessary, whichever occurs first.

Assessments should be made at each visit (or more frequently, if necessary) of any changes in severity, the relationship to the study drug, the intervention required to treat it, and the outcome.

Common side effects known for CX-01 are provided in the IB (63). All AEs will be immediately recorded in the patient's source documents.

6.6.3.2.2 Definition of an Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose either:

- Results in death
- Is life-threatening
- Requires patient hospitalization or prolongation of an existing hospitalization. Note: Hospitalization for the purpose of administration of induction or consolidation treatment will not be considered an AE
- Results in a persistent or significant disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life function)
- Is congenital anomaly or birth defect
- Is another medically important serious event as judged by the Investigator.

Note: The term '***life-threatening***' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalization is defined as the patient being hospitalized overnight, or the patient's hospital stay being prolonged for at least an additional overnight stay. Hospitalizations for safety reasons, e.g., an overnight stay to avoid a repeat journey, or patients undergoing a preplanned hospital procedure, will not be considered an SAE. Hospitalizations or prolongation of hospitalization for a procedure will be noted in the eCRF. Hospitalization for the purpose of administration of induction or consolidation treatment will not be considered an AE.

Important medical events that may 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 included 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.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the client.

Medical and scientific judgment should be exercised in deciding whether an AE should be reported as an SAE in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

Any AE leading to death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of study treatment which is felt to be related to the study drug must be reported as an SAE.

Toxicities which fall within the SAE definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not, with the exception of hospitalization for induction, re-induction or consolidation treatment for AML. Toxicities unrelated to treatment that do NOT fall within the SAE definitions above, must be documented as AEs in the patient's source documents and eCRF.

6.6.3.2.3 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB. Suspected adverse reactions means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.

6.6.3.2.4 Follow-up of Adverse Events/Serious Adverse Events

Adverse events will be followed until resolution or stabilization of the event, completion of the patient's participation, or study termination, or the Investigator or designee and Sponsor agree that follow-up is no longer necessary, whichever occurs first.

Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator or designee and Sponsor agree that follow-up is no longer necessary.

All AEs will be immediately recorded in the patient's source documents.

6.6.3.2.5 Assessment of Severity

The severity grade will be based on the NCI-CTCAE version 4.03. An electronic copy of the CTCAE Version 4 can be downloaded from: http://safetyprofiler-

ctep.nci.nih.gov/CTC/CTC.aspx.

6.6.3.2.6 Causality Assessment

The Investigator must assess and document causal relationship between an SAE and the study drug on the basis of his/her clinical judgment using the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

Is there a "reasonable possibility" the drug caused the AE (meaning there is evidence to suggest a causal relationship between the drug and the AE)?

- Yes
- No.

Could the AE be explained by underlying disease or other drugs or chemicals?

- Yes
- No.

6.6.3.2.7 Action Taken Regarding the Study Drug

- **No action taken**: no change in treatment dosage
- **Dose reduction**: study drug dosage adjusted/or and reduced
- **Drug interrupted**: study drug temporarily stopped
- **Drug withdrawn**: study drug permanently stopped
- **Specific treatment instituted**: other concomitant medication or non-drug therapy administered in response to an AE.

6.6.3.2.8 Adverse Event Outcome

- **Recovered/resolved**: the patient fully recovered from the AE with no residual effect observed
- **Recovered/resolved with sequelae**: the residual effects (e.g., symptoms or pathology) of the AE are still present and observable
- **Not recovered/not resolved**: the AE itself is still present and observable
- **Fatal**: the patient dies as a result of the AE

- **Unknown**: outcome of the AE is unknown.

6.6.3.3 Pregnancy

Although not considered an AE, it is the responsibility of the Investigator or their designee to report any pregnancy in a patient or the patient's sexual partner that occurs during the study. All patients who become pregnant must immediately discontinue the study drug and be withdrawn from the study. The patient will be followed to completion/termination of the pregnancy. This information is important for both drug safety and public health concerns. If a patient is found to be pregnant after the study treatment was administered, the Investigator should report this to the CRO and Sponsor immediately and document using the Pregnancy Form.

The Investigator must make every effort to follow the patient until completion of pregnancy. If the outcome of pregnancy meets the criteria for classification of an SAE, the Investigator must follow the procedures for reporting SAEs outlined in Section 6.6.4.

6.6.3.4 12-lead Electrocardiogram

A standard resting 12-lead ECG will be performed at Screening and at the end of induction (Day 7). Additional 12-lead ECGs may be obtained at the Investigator's discretion or if clinically indicated.

6.6.3.5 Left Ventricular Ejection Fraction

An echocardiography or MUGA scan will be performed during Screening to determine the patient's cardiac ejection fraction for eligibility in the study.

6.6.3.6 Laboratory Assessments

The time points at which these samples will be collected are shown in the Schedule of Study Procedures (Table 6—1) and (Table 6—2). Assessments will be performed and evaluated locally.

The following clinical laboratory assessments will be performed:

- **Hematology panel**: hemoglobin , ANC, and platelet
- **Chemistry (comprehensive metabolic panel)**: ALT, AST, total bilirubin, alkaline phosphatase , BUN, and serum creatinine
- **Coagulation panel**: anti-factor Xa, PT, aPTT, INR.

Any clinically significant abnormal laboratory value should be immediately re-checked whenever possible, for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE per protocol requirement.

A urine pregnancy test will be conducted at Screening for all females of childbearing potential to confirm absence of pregnancy. Positive urine test results must be confirmed by serum pregnancy test. Results will be analyzed locally. Pregnancy tests may be performed at other visits at the discretion of the Investigator.

6.6.3.6.1 Bone Marrow Aspirate/Biopsy

To evaluate disease status, a bone marrow aspirate and biopsy if needed will be done within 28 days before starting therapy. Bone marrow aspirate and biopsy will also be performed between Days 14-21 to determine the need for re-induction chemotherapy (see Section 6.4.1). Subsequent bone marrow examinations are specified in Section 6.5.1. Bone marrow aspirate at baseline and follow-up should include analysis by flow cytometry and cytogenetic analysis. Bone marrow (or peripheral blood if bone marrow is unavailable) should be sent to the institution's local cytogenetic laboratory for analysis.

For patients with documented CR, confirmatory bone marrow aspirate slides will be submitted to the Sponsor or designee.

6.6.3.7 Vital Signs and ECOG Performance Status

Measurement of vital signs will include an assessment of heart rate, BP, height, and weight. Height will be measured once during Screening. Weight will be measured at the beginning of each cycle to calculate treatment doses. Vital signs may be repeated for clinically significant abnormal findings at the discretion of the Investigator.

Eastern Cooperative Oncology Group performance status will be collected at Screening Visit only (see Appendix B).

6.6.3.8 Physical Examination

All abnormal findings on physical exam will be documented in the source documentation and eCRF. New or worsened abnormalities should be recorded as AEs, if applicable.

6.6.4 Reporting Serious Adverse Events

All SAEs will be collected from the time of informed consent until 30 days after the last study treatment and regardless of study drug relationship, must be reported by facsimile to the CRO within 24 hours of knowledge of the event. The facsimile report should include all available information requested on the SAE form (refer to Key Study Personnel page for fax number to report SAEs).The SAE form will collect data surrounding the event, e.g., the nature of the symptom(s), time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued. The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic reports, and procedures, as well as all pertinent medical information

related to the event, will also be collected.

The CRO will forward SAE queries directly to the site requesting incomplete or missing information. It is the Investigator's responsibility to be diligent in providing this information back to the CRO as soon as it is available. Initial reports of SAEs should not be left on telephone voicemails. Always fax SAE reports and follow-up with a telephone call if needed.

All sites will follow their institutional requirements for submission of SAEs to their IRB.

6.6.4.1 Expected Adverse Events

Myelosuppression and its associated complications due to underlying leukemia and/or intensive anti-leukemia therapy are expected events during therapy for AML.

Hospitalization or prolongation of hospitalization for the treatment of the following events that are known to be associated with myelosuppression from leukemia and/or intensive leukemia therapy, are also considered to be expected. These events still need to be recorded as AEs on the eCRF:

- Fatigue, weakness and/or shortness of breath associated with anemia
- Febrile neutropenia
- Bleeding due to thrombocytopenia e.g., epistaxis, gastrointestinal bleeding
- Bacteremia, sepsis, or other infections
- Neutropenic colitis.

Death due to progression of AML and/or its associated complications are expected in the patient population and are listed in Appendix E. Deaths should be reported with Investigator's assessment of causality.

Appendix E also contains a list of known/expected AEs for cytarabine and idarubicin. The IB contains expected events known for CX-01 (63).

6.6.4.2 Investigator's Notification of the Sponsor

All Investigators will be thoroughly instructed and trained on all relevant aspects of the Investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the Investigator site file. This information will be updated as needed. Serious AEs occurring during the study must immediately (within 24 hours of Investigator's awareness) be reported per Section 6.6.4 to the recipient detailed in the manual.

Serious AEs occurring after the protocol-defined observation period will be processed by

the Sponsor according to all applicable regulations.

6.6.4.3 Notification to the Independent Review Board

Notification to the IRB about all relevant events (e.g., SAEs, SUSARs) will be performed by the Sponsor or Sponsor's designee and/or by the Investigator according to all applicable rules/regulations.

6.6.4.4 Notification to the Authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the Sponsor or Sponsor's designee and/or by the Investigator according to all applicable rules/regulations.

6.6.4.5 Sponsor's Notification to the Investigational Site

The Sponsor or designee will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations. The Sponsor or Sponsor's designee will send SUSARs to a site once the site initiation visit has occurred and will stop sending SUSARs to a site once the last subject End of Treatment Visit for that site (30 days after last dose) occurs.

6.6.5 Data and Safety Monitoring Committee

A DSMC will serve as a monitoring advisory group for the study. The primary role for the DSMC will be to examine the safety and efficacy throughout the duration of the study.

The DSMC will be created to further protect the rights, safety, and well-being of patients who will be participating in the study by monitoring their progress and their results. The DSMC comprises qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The DSMC will be described in detail in the DSMC Charter.

The DSMC will monitor data during the study. All activities of the DSMC will be documented. This documentation will contain data summaries and analyses provided to the committee as well as minutes of any ad-hoc meetings, as necessary.

6.6.6 Pharmacokinetics

Steady-state PK samples will be collected at selected sites only. Pharmacokinetic samples will be collected during the induction cycle on Days 3 and 5.

The first 6 patients assigned to a CX-01 dose level (low; 0.125 mg/kg/hour, intermediate; 0.25 mg/kg/hour, and high doses; 0.325 mg/kg/hour) will have PK's drawn (consistent with the original protocol which included 4 dose groups).

The same 6 patients that participate in Day 3 PK sampling will have one additional blood sample drawn on Day 5 of treatment. The PK samples may be drawn before the CX-01 infusion is stopped to change the CX-01 bag and tubing. All PK blood samples must be drawn from the opposite arm to the CX-01 IV infusion.

The site will document actual dates and times of sample collection in the source documents and eCRF. Any reason for missed or lost samples should be recorded.

Pharmacokinetic blood samples will be processed and may be batch shipped for analysis to a bioanalytical laboratory. Full details of sample handling and shipment can be found in the Study Operations Manual (also refer to Appendix F for details).

6.7 Data Quality Assurance

The Sponsor or Sponsor's designee performs quality control and assurance checks on all clinical studies that it conducts. Before enrolling any patients in this study, the Sponsor or Sponsor's designee and the Investigator will review the protocol, the IB, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. The Sponsor's designee will monitor the conduct of the study at the site and will verify eCRFs against source documents. Additionally, the Sponsor's designee will use automated validation programs to help identify missing data, selected protocol deviations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the Investigator for resolution.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor or Sponsor's designee. Inspection of site facilities (e.g., pharmacy drug storage areas, laboratories, etc.) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

6.8 Statistical Methods

6.8.1 Determination of Sample Size

A total of 25 evaluable patients per arm will provide 71.8% power for each test comparing a dose with control via a Fisher's exact test at 1-sided alpha = 0.15 to detect a difference between a control proportion 0.55 and an experimental dose proportion 0.80; these tests will be conducted in a fixed sequence: higher dose versus control first and lower dose versus control second, with the second test considered exploratory (failed) if the first test fails.

6.8.2 Patient Populations Analyzed

The analysis sets that will be used for statistical analyses are as follows:

Intent-To-Treat (ITT): All randomized patients. Patients will be analyzed according to the treatment to which they are randomized. The ITT Population will be the primary analysis set for the efficacy variables.

Per Protocol (PP): Supporting analyses will be conducted on the PP Population, comprising all patients randomized and treated without major protocol violations during the trial. This population will be documented before final database lock.

Safety: All patients who received at least one dose of study treatment. Patients will be included in the analyses according to the treatment they received. The Safety Population will be used in the analyses of all safety endpoints.

6.8.3 General Considerations

The following is an overview of the statistical analysis methods to be used in this study. Details on the statistical analyses will be given in the Statistical Analysis Plan (SAP). Patients will be randomized to one of the following treatment groups in a 1:1:1 ratio:

- **Group 1**: Idarubicin + Cytarabine, OR
- **Group 2**: Idarubicin + Cytarabine plus lower dose CX-01 (0.125 mg/kg/hour), OR
- **Group 3**: Idarubicin + Cytarabine plus higher dose CX-01 (0.25 mg/kg/hour)

Unless stated otherwise, descriptive summary statistics will include frequency counts and percentages for categorical variables and number of observations, mean, standard deviation (SD), median, minimum and maximum and the 1st and 3rd quartiles for continuous variables.

The final analysis will be done when the last patient completes the study treatment, all assessments for disease response, and a Safety Follow-Up Visit approximately 30 days after termination of study treatment. All patients will be followed for OS for at least 18 months. Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

6.8.4 Demographics and Other Baseline Characteristics

6.8.4.1 Patient Disposition

The number and percentage of patients screened, randomized, and treated will be presented by treatment group. The reasons for patients discontinued from the treatment will be summarized by study stage and treatment group. In addition, the number of patients screened and included in each analyses population will be displayed by center.

6.8.4.2 Patient and Disease Characteristics

Descriptive summaries of demographics and baseline characteristics will be presented by treatment group and overall for the Safety, ITT, and PP Populations. Comparability of the treatment groups with respect to demographic and baseline characteristics will be assessed using the descriptive summaries.

The following demographic data will be summarized:

- Age at Screening (years)
- Race and ethnicity
- Height (cm)
- Weight (kg) at baseline.

The following baseline characteristics will be summarized:

- Stage of AML at diagnosis
- Time since diagnosis
- Baseline blasts in bone marrow (%)
- Baseline peripheral blasts
- ECOG performance status
- Baseline LDH

6.8.5 Medical and Surgical History

Medical and surgical history includes relevant history other than AML. This information will be coded using the version of MedDRA currently in effect at the time of database lock.

6.8.6 Concomitant Therapy

All non-study medications taken during the study will be coded using the World Health Organization Drug Dictionary (WHO-DD) and the Anatomical Therapeutic Chemical classification system. Coding will include the drug class and generic drug name. Non-study medications taken during the study will be categorized as prior medications, concomitant medications, and post treatment medications. Prior medications will be defined as non-study medication with a stop date prior to the first dose of study treatment.

Post treatment anti-AML therapies will be coded and summarized.

6.8.7 Extent of Study Drug Exposure and Compliance

Extent of study drug exposure will be summarized for the entire study treatment period and by cycle. Exposure variables will include duration of study treatment, number of dose reductions, number of treatment delays, number of treatment cycles, and dose intensity relative to dose levels specified in the protocol.

6.8.8 Efficacy Analysis

6.8.8.1 Primary Efficacy Outcome Measure

The primary efficacy analysis will be performed on the ITT Population as defined in Section 6.8.2. Fisher exact test will be used to compare the proportion of CRs between each dose and control.

6.8.8.2 Secondary Efficacy Outcome Measures

The primary analysis will be repeated using the PP Population as a supportive analysis. Complete response rates and confidence intervals will also be reported for key subgroups (e.g., randomization strata). Analyses of EFS, LFS, time to neutrophil and platelet recovery, and OS will be descriptive. Kaplan-Meier (KM) estimates will be used to estimate the survival distribution for each arm and KM plots will be produced to accompany these analyses. Confidence Intervals will be reported for medians and KM estimates. Duration of response will be analyzed using a similar approach; the analysis will account for the competing risk of death and the survival distributions will be estimated as cumulative incidence functions.

Mortality rate at Day 30, Day 60, and Day 90 will be reported using descriptive statistics in a manner similar to the reporting of the morphologic CR rate. The time to neutrophil and platelet recoveries will be reported using the following descriptive statistics: N, mean, SD, median, minimum, maximum, and the 1st and 3rd quartiles.

6.8.9 Subgroup Analysis

Subgroup analyses will be defined in the SAP. All results from these analyses are deemed to be exploratory. Exploratory analysis will be descriptive.

6.8.10 Safety Analysis

Safety analysis will be descriptive based on the Safety Population and will involve examination of descriptive statistics and individual patient listings for effects of study treatment on clinical safety and tolerability. The safety assessment period is from the first dose of study treatment until 30 days following the last dose of study treatment.

6.8.10.1 Adverse Events

All AEs will be categorized by SOC and Preferred Term using the MedDRA dictionary

and graded according to NCI-CTCAE v4.03. Treatment-emergent AE summaries will include NCI-CTCAE Grade 3 or higher AEs, and AEs resulting in discontinuation of study treatment, AEs resulting in death, deaths during the treatment period within 30 days of the last study treatment, deaths reported beyond 30 days that are considered study drug-related, and the incidence of laboratory values with NCI-CTCAE Grades 3 or 4. Particular attention will be upon coagulation parameters and bleeding-related events.

6.8.10.2 Clinical Laboratory Assessments

Clinical laboratory assessment will be summarized using frequency tables, shift tables, and descriptive statistics. Frequency tables and shift tables will be presented by NCI-CTCAE grade. Laboratory variables with no NCI-CTCAE group will be presented in shift tables with respect to normal range. All laboratory variables will be presented in tables of descriptive statistics (mean, SD, etc.) and in graphs.

6.8.10.3 Vital Signs and ECOG Performance Status

Vital signs variables and ECOG performance status will be summarized using descriptive statistics.

6.8.10.4 Electrocardiogram

Electrocardiogram will be summarized using descriptive statistics.

6.8.11 Pharmacokinetic Analysis

The PK parameters will be summarized by descriptive statistics. A list of PK parameters and definitions will be specified in the SAP.

7. RISKS AND BENEFITS

The potential risks associated with participation in this study are minimal based on available safety data. Such risks are limited to unforeseen adverse interactions between idarubicin + cytarabine and CX-01. Heparins, as a class are associated with abnormal LFTs, which are generally reversible and of little clinical importance.

Study participants may benefit from participating in the trial if, by mobilizing AML stem cells from the protective environment of the bone marrow or through other mechanisms, the addition of CX-01 at either of two dose levels results in an enhanced cytotoxic effect of idarubicin + cytarabine, although such benefit is not guaranteed.

For further details concerning warnings, precautions, and contradictions, refer to the appropriate section of the IB (63).

8. INVESTIGATORS REGULATORY OBLIGATIONS

8.1 Pre-study Documentation

The Investigator must provide the Sponsor or designee with the following documents BEFORE consenting any patients:

1. All applicable regulatory forms
2. Current signed and dated curricula vitae for the Investigator, sub-Investigators, and all key personnel listed on the clinical study information form
3. Copy of the IRB approval letter for the protocol and informed consent
4. Copy of the IRB-approved ICF to be used
5. When applicable, a list of the IRB members and their qualifications, and a description of the committee's working procedure
6. Copy of the protocol signature page signed by the Investigator
7. Fully executed clinical study agreement (CSA)
8. Completed FDA Form 1572.

8.2 Electronic Data Capture

The CRO will supply the investigational site with access to a web based EDC computer system. Edit checks and data logic checks are at the point of entry and are validated according to company standard operating procedures. All data entered into the system are transferred to a secure database maintained by the CRO.

Access to the EDC system at the site, for vendors, at the Sponsor, and at the CRO is password protected. Study access is granted to site personnel only after they have been trained in the use of the EDC system by web based training at the investigational site.

The EDC system contains a system generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available at the Investigator's site, at the CRO, and at the Sponsor.

Data entries made in the EDC screens should be completed within 5 days of the patient's study visit and must be supported by source documents maintained for all patients enrolled in the study.

The data collection tool for this study will be the validated electronic system. Patient data necessary for analysis and reporting will entered and transmitted via the electronic system. Clinical data management will be performed in accordance with applicable

standards and data cleaning procedures. For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

At the conclusion of the study all data will be delivered to the Sponsor.

8.3 Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in Section 6.6.3.1. Furthermore, the Investigator is responsible for ensuring that any sub-Investigator promptly brings AEs to the attention of the Investigator. If applicable, the Investigator is also responsible for informing the site's IRB of all SAEs (per IRB requirements).

8.4 Review of Source Records

The Investigator agrees that the Study Monitor (and other qualified personnel as appropriate) will be allowed to conduct site visits to the investigational facilities for the purpose of reviewing source records pertinent to the study. The Investigator will make the study files available during monitoring visits. These files will also be available for inspection by representatives of the Sponsor, competent authorities and/or the IRB. Patients will not be identified by name on any of the study documents utilized by the Sponsor for their analysis, and confidentiality of information in medical records will be preserved. Every effort will be made to maintain the confidentiality of the patient unless disclosure is required by regulations.

8.5 Monitoring of the Study

The Study Monitor will be responsible for monitoring this clinical trial. The Study Monitor will monitor the study conduct, proper eCRF completion, source documentation completion and retention, and accurate study drug accountability. The Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication with the site. It is essential that the Study Monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visits to answer questions, and to provide any missing information.

8.6 Protocol Amendments

Any substantial amendments in the research protocol during the period, for which the IRB approval had already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the Investigator in the interest of preserving the safety of all patients included in the trial.

8.7 Protocol Deviations

A protocol deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Investigational sites will report protocol deviations to their IRB per institutional reporting requirements.

8.8 Change in Investigator

If any Investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the Sponsor or designee, IRB, or another Investigator. The Sponsor or designee must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation.

8.9 Criteria for Termination of the Study or Study Center/Site

8.9.1 Early Termination of the Study

If the Sponsor or its designee, the Investigator or regulatory agency discovers any condition arising during the study that indicate that the study or the study site should be terminated, this action may be taken after appropriate consultation between the Sponsor or its designee and the Investigator. The Sponsor or its designee has the right to terminate the participation of either an individual site or the study at any time, for any reason which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study.
- Submission of knowingly false information from the study site to the Sponsor or its designee or regulatory authorities.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to investigational sites regarding the end of study procedures.

8.10 Clinical Study Report

A clinical study report (CSR) will be prepared following the completion of the study.

8.11 Confidentiality

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study may be asked to endorse the final report.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

8.12 Records Retention

Essential documents must be retained for longer than 5 years after completion of the study, 2 years after the final marketing authorization in an ICH region or until at least 2 years have elapsed since the discontinuation of clinical development of the study drug. If it becomes necessary for the Sponsor or the Competent Authority to review any documentation relating to the study, the Investigator must permit access to such records.

Study files may be discarded upon written notification by the Sponsor. To avoid error, the Investigator must contact the Sponsor before destroying any records or reports pertaining to the study, to ensure that retention is no longer required. Other source documents, such as patient's medical records, must be retained for the maximum period of time permitted by the hospital or institution and until such time when the Investigator is informed by the Sponsor that there is no further need to do so.

In addition, in accordance with the Investigator agreement, the Sponsor should be contacted if the site's Principal Investigator plans to leave the investigational site so that appropriate arrangements can be made.

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10. APPENDICES

APPENDIX A – Acute Myeloid Leukemia Response Criteria

The IWG consensus criteria for treatment response in AML will be used to evaluate response to treatment.

Definitions of Remission

Morphologic complete remission (CR): ANC >1000/μL, platelet count >100,000/μL, <5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease.

Morphologic CR with incomplete blood count recovery (CRi): CRi, which is CR without recovery of neutrophils and/or platelets (ANC may be <1000 μL and/or platelet count <100,000/μL).

Partial remission (PR): ANC >1000/μL, platelet count >100,000/μL and at least a 50% decrease in the percentage of marrow aspirate blasts to 5 to 25%, or marrow blasts <5% with persistent Auer rods.

Progressive Disease

Progressive disease (PD) is defined as any one of the following:

- More than 50% increase in bone marrow blast % from best assessment (with a minimum threshold of 20% blasts in the marrow).
- >50% increase in circulating malignant blasts (with absolute blasts >1000/μL).
- Development of biopsy-proven extramedullary leukemia (if the patient has extramedullary disease at baseline then PD will be defined by blood and marrow criteria or if new sites of extramedullary disease appear).

In patients who present with initial marrow blast percentage sufficiently high to preclude the ability to base disease progression on a >50% increase in marrow blast percentage; disease progression should be based on peripheral blood criteria or development of extramedullary leukemia.

Stable Disease

Patients who fail to achieve CR, CRi or PR and who do not have criteria for PD will be defined as having stable disease. If the patient dies prior to response assessment at the end of Cycle 1, then they will be classified as “Indeterminate”.

Relapse from CR or CRi

Reappearance of leukemia blasts in the peripheral blood; or >5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aphasia); or appearance or reappearance of extramedullary disease and the bone marrow blast percentage is >5% but < or equal to 20%, than a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is >5% is necessary to establish relapse.

APPENDIX B – ECOG Performance Score

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

Source: As published in Am. J. Clin. Oncol. (CCT) 1982; 5:649-655.

APPENDIX C – Estimated Creatinine Clearance – Cockcroft Gault Formula

(As published in Nephron 1976; 16:31-41)

$$Cl_{cr} = \frac{(140 - age) \times BM \times GF}{S_{cr} \times 72}$$

BM = body mass (kg)

GF = gender correction factor (0.85 in females; 1.00 in males)

S_{cr} = serum creatinine (mg/dL)

APPENDIX D – Child-Turcotte-Pugh Classification of Severity of Cirrhosis

Parameter	Points Assigned		
	1	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin	<2 g/dL (<34.2 micromol/liter)	2 to 3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8 to 3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Source: website: www.uptodate.com, accessed 12 March 2015.

Modified Child-Turcotte-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%, and class C: 45 and 35%.

APPENDIX E – Expected Adverse Events for Cytarabine and/or Idarubicin

For this protocol only, certain AEs/Toxicity Grades are exceptions to the Expedited Reporting Guidelines because the AEs are considered as "Expected" with the administration of cytarabine and idarubicin. The following AEs must be reported through the routine AE or SAE reporting mechanism, as appropriate:

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
Blood & Lymphatic	Bone marrow suppression/failure	1-4	❒ cytarabine ❒ idarubicin
	Neutropenia Febrile neutropenia	1-4 3-4	❒ cytarabine ❒ idarubicin
	Thrombocytopenia	1-4	❒ cytarabine ❒ idarubicin
	Pancytopenia	1-4	❒ cytarabine ❒ idarubicin
	Reticulocyte count, decreased	1-4	❒ cytarabine ❒ idarubicin
	Hemorrhage/bleeding (secondary to thrombocytopenia)	1-4	❒ cytarabine ❒ idarubicin
	Anemia Anemia (megaloblastic)	1-4 1-2	❒ cytarabine ❒ idarubicin
General Disorders	Fatigue	1-3	❒ cytarabine ❒ idarubicin
	Fever	1-4	❒ cytarabine ❒ idarubicin
	Chills	1-3	❒ cytarabine ❒ idarubicin
	Injection site reaction/cellulitis, pain, stinging or burning sensation, inflammation	1-4	❒ cytarabine ❒ idarubicin

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
	Tissue necrosis (if extravasation)	3-4	❒ cytarabine ❒ idarubicin
	Infections	1-4	❒ cytarabine ❒ idarubicin
	Edema/swelling	1-3	❒ cytarabine ❒ idarubicin
Respiratory, Thoracic and Mediastinal Disorders	Pulmonary toxicity	1-4	❒ cytarabine ❒ idarubicin
	Dyspnea	1-4	❒ cytarabine ❒ idarubicin
	Adult respiratory distress syndrome (ARDS)	3-4	❒ cytarabine ❒ idarubicin
	Pulmonary edema	1-4	❒ cytarabine ❒ idarubicin
	Oropharyngeal pain	1-4	❒ cytarabine ❒ idarubicin
	Pulmonary allergy	1-4	❒ idarubicin
	Interstitial pneumonitis	2-4	❒ cytarabine ❒ idarubicin
Gastrointestinal Disorders	Diarrhea	1-4	❒ cytarabine ❒ idarubicin
	Bowel necrosis	3-4	❒ cytarabine
	Necrotizing colitis	3-4	❒ cytarabine
	Abdominal or stomach pain/tenderness/cramping	1-3	❒ cytarabine ❒ idarubicin

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
	(peritonitis)		
	Typhlitis (neutropenic enterocolitis)	3-4	❒ cytarabine ❒ idarubicin
	Pneumatosis intestinalis	1-4	❒ cytarabine
	Nausea	1-3	❒ cytarabine ❒ idarubicin
	Vomiting	1-4	❒ cytarabine ❒ idarubicin
	Ulceration/Inflammation: Oral ulcer/stomatitis/mouth, throat Esophageal ulcer/esophagitis Anal ulcer/inflammation Other GI ulceration	1-4	❒ cytarabine ❒ idarubicin
	Pancreatitis	1-4	❒ cytarabine ❒ idarubicin
	Hyperuricemia	1-4	❒ cytarabine ❒ idarubicin
	Mucositis	1-4	❒ cytarabine ❒ idarubicin
Vascular	Hypotension	1-2	❒ cytarabine ❒ idarubicin
Eye Disorders	Corneal toxicity (ocular pain, tearing, foreign-body sensation, photophobia, blurred vision)	2-4	❒ cytarabine ❒ idarubicin
	Hemorrhagic conjunctivitis	1-4	❒ cytarabine ❒ idarubicin

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
Hepatobiliary	Hepatic failure	3-4	❒ cytarabine
	Hepatic function, abnormal	3-4	❒ cytarabine ❒ idarubicin
	Liver abscess/ injury	3-4	❒ cytarabine
	Jaundice (hyperbilirubinemia)	3-4	❒ cytarabine ❒ idarubicin
	Aplasia	1-4	❒ idarubicin
Cardiovascular	Cardiomyopathy	1-4	❒ cytarabine ❒ idarubicin
	Cardiomegaly	1-4	❒ cytarabine ❒ idarubicin
	Congestive heart failure (CHF)		❒ idarubicin
	Left ventricular ejection fraction (LVEF), decreased	2-4 Use %drop from baseline	❒ idarubicin
	Arrhythmias (atrial fibrillation/others)	1-4	❒ idarubicin
	Abnormal ECG	1-4	❒ cytarabine ❒ idarubicin
	Cardiac arrest	4	❒ cytarabine ❒ idarubicin
	Chest pain	1-3	❒ cytarabine ❒ idarubicin
	Myocardial infarction	2-4	❒ cytarabine

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
			❒ idarubicin
Infections and Infestations	Infection (secondary to neutropenia/granulocytopenia)	2-4	❒ cytarabine ❒ idarubicin
	Sepsis	4	❒ cytarabine ❒ idarubicin
	Pneumonia	2-4	❒ cytarabine ❒ idarubicin
Immune System Disorders	Anaphylaxis/Allergic edema	1-4	❒ cytarabine ❒ idarubicin
Metabolism	Anorexia (decreased appetite)	2-4	❒ cytarabine ❒ idarubicin
Investigations/ Laboratory Abnormalities	ALT	1-4	❒ cytarabine ❒ idarubicin
	AST	1-4	❒ cytarabine ❒ idarubicin
	Alkaline Phosphatase	1-4	❒ cytarabine ❒ idarubicin
	GGT	1-4	❒ cytarabine ❒ idarubicin
	Bilirubin, increased	1-4	❒ cytarabine ❒ idarubicin
	Creatinine, increased	2-4	❒ idarubicin
	Uric acid, increased	1-4	❒ cytarabine ❒ idarubicin
	Proteinuria	1-3	❒ cytarabine ❒ idarubicin
	Electrolyte abnormalities	1-4	❒ cytarabine ❒ idarubicin

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
	Platelet count, decreased	1-4	❒ cytarabine ❒ idarubicin
	WBC, decreased	1-4	❒ cytarabine ❒ idarubicin
Musculoskeletal, Connective Tissue and Bone Disorders	Myalgias & Arthralgias (muscle pain/joint pain)	1-3	❒ cytarabine ❒ idarubicin
	Cytarabine Syndrome: Fever, myalgia, bone pain, chest pain, rash, conjuncitvities and malaise 6-12 hours following drug administration.	1-3	❒ cytarabine
Nervous System Disorders [a]	Paresthesia	1-3	❒ cytarabine ❒ idarubicin
	Sensory peripheral neuropathy and/or motor peripheral neuropathy	1-4	❒ cytarabine ❒ idarubicin
	Neuralgia/neuritis	1-3	❒ cytarabine ❒ idarubicin
	Dizziness	1-3	❒ cytarabine ❒ idarubicin
	Depressed Level of Consciousness (Mental Status Changes)		❒ idarubicin
	Seizures	1-4	❒ cytarabine ❒ idarubicin
	Headache	1-3	❒ cytarabine ❒ idarubicin
	Syncope/fainting	3	❒ cytarabine

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
			❒ idarubicin
	Cerebellar and cerebral dysfunction, including the following AE/SAEs: • Personality changes • Somnolence • Convulsion • Coma • Stroke-like episodes	1-4	❒ cytarabine ❒ idarubicin
Renal & Urinary	Acute kidney injury	1-4	❒ cytarabine
	Renal impairment, disorder	1-4	❒ cytarabine ❒ idarubicin
	Urinary retention	1-4	❒ cytarabine ❒ idarubicin
	Hemolytic uremic syndrome	1 or 3	❒ cytarabine ❒ idarubicin
	Hyperuricemia	1,3-4	❒ cytarabine ❒ idarubicin
Skin	Alopecia	1-2	❒ cytarabine ❒ idarubicin
	Rash	1-3	❒ cytarabine ❒ idarubicin
	Hand-foot syndrome/Palmar plantar erythrodysaesthesia (PPE) (redness, swelling, pain on palms of hands/soles of feet	1-3	❒ cytarabine ❒ idarubicin
	Ulceration, skin	1-4	❒ cytarabine

CTCAE Category	Adverse Event	Grade	Chemotherapy Attribution
	Desquamation, peeling, scaly, exfoliation of skin	1-4	❒ cytarabine
	Urticaria/Hives, skin	1-3	❒ cytarabine ❒ idarubicin
	Pruritis, skin	1-3	❒ cytarabine
	Freckling, skin	1-3	❒ cytarabine
Reproductive and Fertility	Teratogenicity, Embryotoxicity	4	❒ cytarabine ❒ idarubicin
	Sperm abnormalities	4	❒ cytarabine
Congenital	Distal limb defects (upper and lower extremities) Ear deformities	4	❒ cytarabine ❒ idarubicin

APPENDIX F – Blood Sample Handling

Blood sample collection procedure, and sample process, storage and shipment

- The study site will be provided with 4.5 mL tubes with 3.2% trisodium citrate
- Draw and fill the 4.5 mL tube containing 3.2% trisodium citrate (completely fill with blood to minimize citrate dilution)
- Within 30 minutes of collection, centrifuge tube for 15 minutes at 3000 g at 16°C/ 60.8ºF. **Blood samples must be kept on ice until they are centrifuged (a delay in centrifuging and separating plasma should not exceed one hour because the platelet factor leaches out of platelets and binds CX-01 resulting in erroneous CX-01 values)**
- Using a plastic pipette, transfer 2 mL of plasma from the tube into two provided cryogenic vials; 1 mL in each tube. Each of the two 1 mL-cryogenic vials must be labeled:

  "**CX-01 concentration**" and will also include: The sample #, patient's randomization/Study ID #, Initials, Study site #, Protocol # (CNTX-CX-01-2015-AML-2) and collection date/time.

- Labeled 1 mL/cryogenic tubes must be stored immediately in a -60°C to 80°C freezer

Once the full set of blood samples from a patient is complete, all the resulting vials must be shipped under cryogenic conditions (dry ice) to the bioanalytical laboratory (see Study Operations Manual for name of lab and notification number).

Please call the bioanalytical laboratory to notify them prior to shipments. Please ship specimens via FedEx only on Monday, Tuesday or Wednesday to prevent thawing and sample loss.