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CPX-351 (Cytarabine:Daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

Lancet, et al

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Re: 17-14026 – CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed Secondary AML

This supplement contains the following items:

1. Original and final study protocol for CLTR0310-301
2. Original and final statistical analysis plan for CLTR0310-301

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Protocol CLTR0310-301


**PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS
CYTARABINE AND DAUNORUBICIN IN PATIENTS 60-75 YEARS OF AGE
WITH UNTREATED HIGH RISK (SECONDARY) AML.**

SPONSOR


Celator Pharmaceuticals, Inc.



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Celator Pharmaceuticals, Inc.



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Version 1.0 May 22, 2012

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CPX351.C.PRTCL.00004.v1

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I further agree to conduct the clinical trial referred to above in accordance with all applicable government regulations, Good Clinical Practice, the Sponsor's guidelines and the procedures described in the protocol.

Investigator Signature

Date

Print Name

SIGNATURE PAGE FOR CELATOR PHARMACETICALS, INC.

Protocol: Protocol CLTR0310-301

Title: **PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS
CYTARABINE AND DAUNORUBICIN IN PATIENTS 60-75 YEARS OF
AGE WITH UNTREATED HIGH RISK (SECONDARY) AML**

Approved by the following:

Chief Medical Officer
Celator Pharmaceuticals, Inc.

Signature

Date

PROTOCOL SYNOPSIS

Title:

PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS CYTARABINE AND
DAUNORUBICIN IN PATIENTS 60-75 YEARS OF AGE WITH UNTREATED HIGH RISK
(SECONDARY) AML.

Sponsor:

Celator Pharmaceuticals, Inc.

Objectives:

Primary

- To confirm the efficacy of CPX-351 compared to “7+3” as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.
- To confirm the safety of CPX-351

Secondary

- To confirm the improvement in achievement of morphologic leukemia free state¹
- To confirm post-induction response (CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare pharmacoeconomic differences between the treatment arms

Study Design:

This study is an open-label, parallel arm, randomized study where newly diagnosed AML including t-AML, AML in patients with a history of MDS or CMMoL, and de novo AML in patients with specific adverse karyotypic changes (per WHO definitions) are randomized to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). Patients are stratified by age and AML subtype at randomization to balance these prognostic factors across treatment arms:

Stratification Scheme:

Strata	
Age	Age 60-69 years OR Age 70-75
AML Type	<ul style="list-style-type: none">• Therapy-related AML: t-AML• MDS transformed to AML with prior HMA treatment: _{MDS}AML• MDS transformed to AML without prior HMA treatment: _{MDS}AML• CMMoL transformed to AML: _{CMMoL}AML• De novo AML with MDS karyotype: _{de novo}AML

Study enrollment duration is expected to be approximately 20 months. Efficacy and safety will be compared between the two study arms. Pharmacokinetic samples, at prespecified timepoints, will be collected in every CPX-351 patient.

Sample Size:

Two hundred forty (240) patients will be randomized with equal allocation between arms to obtain a minimum of 220 evaluable patients: 110 in the CPX-351 arm and 110 in the 7+3 arm.

Inclusion Criteria:

- Ability to understand and voluntarily give informed consent
 - Age 60-75 years at the time of diagnosis of AML
-

- Pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow)
- Confirmation of:
 - Therapy related AML: t-AML must have a documented history of prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease
 - AML with a history of myelodysplasia: _{MDS}AML must have bone marrow documentation of prior MDS
 - AML with a history of CMMoL: _{CMMoL}AML must have bone marrow documentation of prior CMMoL
 - De novo AML with karyotypic abnormalities characteristic of MDS: _{de novo}AML must have cytogenetics with abnormalities per WHO.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Able to adhere to the study visit schedule and other protocol requirements
- Laboratory values fulfilling the following:
 - Serum creatinine < 2.0 mg/dL
 - Serum total bilirubin < 2.0 mg/dL, patients with Gilbert's Syndrome should contact the medical monitor
 - Serum alanine aminotransferase or aspartate aminotransferase < 3 times the ULN Note: If elevated liver enzymes, above the ULN, are related to disease; contact medical monitor to discuss.
- Cardiac ejection fraction $\geq 50\%$ by echocardiography or MUGA
- Patients with second malignancies in remission may be eligible if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic chemotherapy, documented by imaging, tumor marker studies, etc., at screening. Patients maintained on long-term non-chemotherapy treatment, e.g., hormonal therapy, are eligible.

Exclusion Criteria:

- Except for CMMoL, patients with history of myeloproliferative neoplasms (MPN) (defined as a history of essential thrombocytosis or polycythemia vera, or idiopathic myelofibrosis prior to the diagnosis of AML) or combined MDS/MPN are not eligible.
 - Acute promyelocytic leukemia [t(15;17)] or favorable cytogenetics, including t(8;21) or inv16 if known at the time of randomization.
 - Clinical evidence of active CNS leukemia
 - Patients with active (uncontrolled, metastatic) second malignancies are excluded.
 - 5.1.2.5 Prior treatment intended for induction therapy of AML; only hydroxyurea is permitted for control of blood counts. For example, a patient with MDS that changes HMA dose and schedule after the diagnosis of AML is excluded. AML-type therapy, such as cytarabine alone ($>1\text{g}/\text{m}^2/\text{day}$) or cytarabine plus an anthracycline as well as prior HSCT are also excluded.
 - Administration of any therapy for MDS (conventional or investigational) must be completed by 2 weeks prior to of the first dose of study drug; in the event of rapidly proliferative disease use of hydroxyurea is permitted until 24 hours before the start of study treatment. Toxicities associated with prior MDS therapy must have recovered to grade 1 or less prior to start of treatment.
 - Any major surgery or radiation therapy within four weeks.
 - Patients with prior cumulative anthracycline exposure of greater than $368\text{ mg}/\text{m}^2$ daunorubicin (or equivalent).
 - Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent
 - Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)
 - Active or uncontrolled infection. Patients with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥ 72 hrs.
 - Current evidence of invasive fungal infection (blood or tissue culture); patients with recent fungal
-

infection must have a subsequent negative cultures to be eligible; known HIV (new testing not required) or evidence of active hepatitis B or C infection (with rising transaminase values)

- Hypersensitivity to cytarabine, daunorubicin or liposomal products
- History of Wilson's disease or other copper-metabolism disorder

Study Drug:

CPX-351 (cytarabine:daunorubicin) Liposome Injection is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio shown to act synergistically in pre-clinical studies. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio.

CPX-351 is provided as a sterile, pyrogen-free, purple, lyophilized product in 50 mL glass, single-use vials. Each 50 mL vial after reconstitution contains 20 mL of CPX-351 (5 units/mL). Each unit (u) contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes suspended in sucrose. Product is stored at $5^{\circ} \pm 3^{\circ}\text{C}$.

Dosage Regimen:

1st Induction

Arm A (CPX-351): Study drug will be given intravenously at $100\text{u}/\text{m}^2$ on days 1, 3 and 5 by approximately 90 minute infusion.

Arm B (7+3): Therapy will be administered intravenously with $100\text{mg}/\text{m}^2/\text{day}$ of cytarabine administered by continuous infusion for 7 days and $60\text{mg}/\text{m}^2$ of daunorubicin given on days 1, 2 and 3.

2nd Induction

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving $>50\%$ reduction in % blasts count on the Day 14 bone marrow assessment. In case the Day 14 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-10 days later, at the discretion of the treating physician, in order to determine effect and need for second induction. Patients who are not expected to receive second inductions include all patients with evidence of aplasia/hypoplasia ($<5\%$ blast count) and patients with equivocal bone marrow results who will have marrow exam repeated. Patients unable to achieve a response (CR+CRi) after two inductions are discontinued from the treatment period and followed for survival.

The second induction uses a modified dose and schedule:

Arm A (CPX-351): Study drug will be given intravenously at $100\text{u}/\text{m}^2$ on days 1 and 3 by approximately 90 minute infusion.

Arm B (5+2): Therapy will be administered intravenously with $100\text{mg}/\text{m}^2/\text{day}$ of cytarabine administered by continuous infusion for 5 days and $60\text{mg}/\text{m}^2$ of daunorubicin given on days 1 and 2.

Consolidation(s)

Only patients with documented response (CR or CRi) are eligible for chemotherapy consolidation. Prior to the first chemotherapy consolidation the LVEF must be documented to be $\geq 50\%$ and prior to every consolidation the PS must be 0-2. A second consolidation course may be given if the first consolidation was well tolerated. Consolidation with stem cell transplant (HSCT) is permitted either in place of chemotherapy consolidation or following chemotherapy consolidation. Consolidation therapy is highly recommended for every patient achieving CR or CRi. First consolidation must be given no earlier than 35 days after the start of the last induction and no later than 75 days after the start of the last induction. Patients must have recovered to $\text{ANC} > 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$ to be eligible for first or second consolidation. The second consolidation is administered 35-56 days after the start of the first consolidation.

Consolidation Dosing

Arm A: CPX-351	
$65 \text{ u}/\text{m}^2$	90 min infusion on Days 1 and 3
Arm B: 5+2	
Cytarabine $100\text{mg}/\text{m}^2$	Continuous Infusion Days 1-5
Daunorubicin $60 \text{ mg}/\text{m}^2$	IV Days 1 and 2

Follow-up

Patients will be followed until death or up to 5 years following randomization. For Event-free Survival (EFS) evaluation, an event is documented as persistent AML after induction or relapse after achievement of CR/CRi or death. After documentation of persistent leukemia or relapse, follow-up for overall survival continues. At the start of HSCT or non-protocol consolidation treatment, AE data collection stops.

Efficacy Variables & Analysis:

- Primary endpoint:
 - Overall Survival (OS)
 - Secondary endpoints:
 - Rate of morphologic leukemia-free state
 - Response rate (CR+CRi), (morphologic, cytogenetic and molecular response)
 - Remission duration (relapse-free survival)
 - Event Free Survival
-

Safety Variables & Analysis:

Patients will be monitored for all clinical adverse events as well as laboratory evaluations.

- Induction Mortality: Day 30 and 60
 - Serious Adverse Events
 - Adverse Events: Grades 1-5 and Grades 3-5
 - Laboratory Evaluations
 - Shift table analyses for hematology and chemistries
 - Time to hematologic recovery and proportion with prolonged cytopenias (≥ 56 days)
 - Copper levels: time to return to baseline levels
 - Cardiac Evaluations
 - Cardiac AEs: Grades 1-5 and Grades 3-5
 - ECG changes (pre and post treatment)
 - LVEF changes (pre and post treatment)
-

Other Variables & Analysis:

PK Sampling for population PK: Patients randomized to CPX-351 are to have samples drawn for population PK. Four samples per patient are taken during the first induction course. CPX-351 patients will be sub-randomized to one of two PK sampling schedules: Schedule 1 Day 1: 45 min, 3 hrs, 8 hrs and prior to dosing on Day 3 (48 hrs (+/- 6 hrs)) or Schedule 2: Day 1: End of Infusion, 2 hrs, 6 hrs and prior to dosing on Day 5 (96 hr (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF.

Serum Copper Sampling: All patients, including those in the control arm, will have serum copper levels assessed at baseline prior to the first dose, after the last induction and at Day 150. The data will be used to assess the variability of serum copper levels in the population as a whole and to determine the proportion of patients with persistently elevated serum copper levels after the end of treatment with CPX-351. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels.

Medical Resource Use: All patients will be assessed for causes and duration of hospitalization. Hospitalization duration associated with first induction, second induction, all inductions, first consolidation, and all consolidations will be assessed. The number of nights and percentage of nights spent in hospital on general wards vs. intensive care settings will be compared as well as duration of hospitalization associated with CR, CRi, and persistent AML. Cumulative hospitalization of Arm A vs. Arm B will be assessed. Similar assessments will be made for red blood cell transfusions, platelet transfusions and supportive care medications (e.g. antibiotics, anti-fungals, anti-virals and growth factors).

Independent Assessments:**Central Review of Diagnosis/Response:**

- Review of hematopathology reports documenting diagnosis of AML, prior AHD and/or chemotherapy exposure
 - FISH or cytogenetics reports documenting karyotypic abnormalities characteristic of
-

myelodysplasia.

- Review of hematopathology and peripheral blood reports documenting response.
- A charter will be reviewed and ratified prior to the initiation of the study

Data and Safety Monitoring Board:

- Consists of at least 2 hematologists + 1 cardiologist + 1 statistician
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and end of study to review day 60 deaths and SAEs
- A single assessment of early deaths will be conducted after 60 patients (30 per arm) have been accrued and followed for 60 days.
- Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB using pre-defined early stopping rules.
- A charter will be reviewed and ratified prior to the initiation of the study

Cardiac Assessments:

- All assessments will be obtained and read locally for patient care. ECHO/MUGA scans will be sent to a central cardiac vendor who will archive the scans for review at a later date. Details will be provided in the cardiac vendor's manual.

Supportive care:

Infection Prophylaxis: is highly recommended during the period of profound neutropenia until ANC returns to 500 or greater. The choice of anti-infectives will be according to institutional protocol.

Growth Factor support: The use of growth factors will be according to institutional protocol.

Transfusion support: The use of transfusion support will be according to institutional protocol.

Statistical Analysis:

This is a randomized phase III study with equal allocation to each of the two treatments, CPX-351 (arm A) and standard of care (7+3, arm B). A total of 220 evaluable patients (110 patients per arm) will be enrolled in this study. Furthermore, we anticipate an accrual rate of 135 evaluable patients per year. An additional 20 patients (10 in each arm) will be accrued to account for ineligibilities and withdrawal of consent.

Primary Endpoint: The primary objective of this study is to compare overall survival (OS), as defined in section 8.2, in all randomized patients. A median OS of 6 months is anticipated in the control arm (Arm B). Assuming exponential survival, 110 patients per arm results in a study with 94% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.60 between the two treatment arms. The analysis for the primary endpoint will be performed after 190 deaths (86%) have occurred. Assuming exponential survival, uniform recruitment of 135 eligible patients per year, 1.65 years of accrual and 1.2 years of follow-up and a median overall survival of 6 months, 190 events are expected to occur within 2.85 years after the opening of the study.

Population PK: Plasma samples for population pharmacokinetic (PK) assessment will be analyzed for concentrations of cytarabine and daunorubicin and their associated metabolites following CPX-351 administration. A population PK modeling approach will be used to describe plasma concentrations for each analyte. In the analysis, a number of covariates, including age, weight, gender, and concomitant medications, will be evaluated to determine if they contribute to differences in the PK estimates among individuals. Details of the analysis will be described in a separate population PK analysis plan

ABBREVIATIONS

7+3	Seven days of continuous infusion of cytarabine at 100 mg/m ² /day and three days of daunorubicin at 60 mg/m ² /day
5+2	Five days of continuous infusion of cytarabine at 100 mg/m ² /day and 2 days of daunorubicin at 60 mg/m ² /day
ADR	Adverse Drug Reaction
AE	Adverse Event
AHD	Antecedent Hematologic Disorders
ALL	Acute Lymphocytic Leukemia
ALT	Alanine Transaminase (SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Ara-U	Arabinosyluracil
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase (SGOT)
ATPase	Adenosine triphosphatase
AUC	Area under the plasma concentration-time curve
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
C _{max}	Maximum plasma concentration
CL	Clearance
CNS	Central nervous system
CPX-351	CPX-351 (cytarabine:daunorubicin) Liposome Injection
CR	Complete Response
CRi	Complete Response with incomplete hematologic recovery
CRF	Case Report Form
CMMoL	Chronic Myelomonocytic Leukemia
CTCAE	Common Terminology Criteria for Adverse Events
d	day
DEHP	di(2-ethylhexyl)phthalate
dL	deciliter
DSMB	Data and Safety Monitoring Board
DSPG	Distearoylphosphatidylglycerol
DSPC	Distearoylphosphatidylcholine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
ELN	European LeukemiaNet
EOI	End of Infusion
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
g	gram(s)
GCP	Good Clinical Practice

HCl	Hydrogen Chloride
HIPAA	Health Information Protection and Portability Act
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HOVON	Hemato-Oncologie voor Volwassenen Nederland
HP	High Purity
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ITT	Intent-to-treat
IRB/EC	Institutional Review Board/Ethics Committee
iv, IV	intravenous
K-M	Kaplan-Meier
L	liter
LDH	Lactate Dehydrogenase
LVEF	Left ventricular ejection fraction
m ²	square meters
MDR	Multi-drug Resistance
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
MLL	Mixed Lineage Leukemia
MPN	Myeloproliferative neoplasm
MLS	Morphologic Leukemia-free State
MRU	Medical Resource Usage
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
mw	molecular weight
N	Number, Population
NF	National Formulary
OS	Overall Survival
PD	Persistent Disease
PhEur	European Pharmacopoeia
PHI	Protected Health Information
PK	Pharmacokinetics
PS	Performance Status
q.s.	quantum sufficiat
RBC	Red blood cells
SAE	Serious Adverse Event
SD	Standard deviation
sAML	Secondary AML
T _{1/2}	Half-life
t-AML	Therapy-related AML
Tmax	Time of occurrence of Cmax
u	Units

μL	Microliter
ULN	Upper Limits of Normal
USP	United States Pharmacopeia
V	Volume
WHO	World Health Organization

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1.0 General Information

This document is a protocol for a human research study. This study is to be conducted according to United States and international standards of Good Clinical Practice (FDA Title 21 parts 11, 50, 54, 56, 312, International Conference on Harmonization and the Declaration of Helsinki), applicable government regulations and Institutional research policies and procedures.

2.0 Background Information

2.1 Acute Myeloid Leukemia in the Elderly and its Treatment

Acute myeloid leukemia represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate and excessive proliferation in the stem cell compartment result in accumulation of non-functional cells termed myeloblasts.²

Untreated AML in all ages is rapidly fatal, with patients dying on average within a few months of diagnosis. Even with treatment, particular groups of AML patients continue to have a poor prognosis. AML in the elderly (age ≥ 60) is associated with increased risk of not responding to therapy and increased risk of dying from the treatment. Appelbaum, et al.³ and Kantarjian, et al.⁴ summarize the factors that contribute to poor outcomes in elderly patients with AML. Risk factors that decrease patient tolerance to therapy or sensitivity of the leukemia to therapy include increasing age, poor performance status, co-morbid medical conditions, accumulated chromosomal abnormalities, adverse mutations, and multi-drug resistance.

There is broad overlap of these risk factors with most elderly AML patients having one or more adverse features. The poor results of treatment in elderly AML lead to a reluctance to treat elderly patients with intensive regimens designed to induce aplasia and complete remission.

Clearing the marrow of leukemia has historically been the only means of obtaining prolonged survival in AML patients. This is usually accomplished by use of intensive cytotoxic/cytoreductive therapy.⁵ The intensity of treatment needed to induce aplasia and complete remission is associated with early mortality rates of 10-20% in elderly patients considered fit for intensive therapy and is higher in patients with co-morbidities and poor performance status.^{3,4,6-8}

Burnett, et al.⁹ published a study of 1273 fit elderly AML patients given intensive therapy. This trial identified cytogenetics, presenting white blood count, age and secondary AML as the main predictors of outcome. Clinical outcomes did not improve with: intensification of induction therapy (daunorubicin 50 mg/m² versus 35 mg/m² and cytarabine 400 mg/m² versus 200 mg/m²), increasing the duration of consolidation from three to four courses, or use of an MDR modulator (PSC-833).

A randomized study reported in 2009 showed that a double induction regimen with 90 mg/m² daunorubicin with cytarabine first induction followed by a second induction with

intermediate dose cytarabine (1 g/m^2) could be safely administered with high rates of complete remission in older patients. The second induction was given even to those who had already achieved CR after first induction, a practice that is not routinely used in the US and Canada. This publication from the HOVON group noted improvement in remission rate when compared to a cytarabine plus 45 mg/m^2 daunorubicin regimen but no improvement in disease-free survival or overall survival was observed.¹⁰ At the present time, the HOVON study has not been replicated in elderly patients by any other group.

Another study by Fernandez, et al., reported success for the same 90 mg/m^2 daunorubicin dose versus 45 mg/m^2 when used for first induction for younger patients.¹¹ If a patient required a second induction, the dose of daunorubicin was reduced to 45 mg/m^2 for all patients. Responding patients were taken to transplant. Neither this study nor the HOVON study used daunorubicin 90 mg/m^2 for second induction courses or in consolidation and neither study demonstrated that 90 mg/m^2 is more effective than 60 mg/m^2 . Although of great interest, neither regimen is ready to be used as the control arm in a comparative study with CPX-351.

The 7+3 regimen using 60 mg/m^2 daunorubicin has been, and continues to be, widely used in the U.S., Canada and the European Union and is supported by a large body of medical literature. Variations on the 7+3 regimen using different anthracyclines, different doses, and different schedules of cytarabine and daunorubicin all lead to the conclusion that this regimen remains acceptable as standard of care for older patients able to tolerate intensive chemotherapy.

The control regimen for this pivotal study with CPX-351 is the 7+3 regimen using $100 \text{ mg/m}^2/\text{d}$ cytarabine by continuous infusion for 7 days and 60 mg/m^2 of daunorubicin on days 1, 2, and 3. Celator proposes daunorubicin as the control anthracycline because that allows a direct comparison of CPX-351 which also delivers daunorubicin. In addition, because both study arms receive cytarabine and daunorubicin this study will be a direct test of whether molar ratio controlled drug delivery can improve antitumor efficacy. Celator also proposes that post-remission chemotherapy be as symmetrical as possible in both arms of the study and plans to reduce the intensity of consolidation with CPX-351 (reduced from 3 to 2 doses and from 100 units/m^2 to 65 units/m^2) to match that of control (7+3 reduced to 5+2). These adjustments in post remission therapy with CPX-351 are intended to result in similar levels of myelosuppression during consolidation therapy.

After complete remission is achieved, leukemic cells likely remain in numbers too small to be detected with current diagnostic techniques. If no further post remission or consolidation therapy is given, almost all patients will eventually relapse.¹² Therefore, post-remission therapy is necessary to eliminate non-detectable disease and prevent or delay relapse. The best consolidation regimen has never been well defined. Generally, the intensity of the standard 7+3 induction therapy is reduced to "5+2" for consolidation, which is a five day continuous infusion of the same dose of cytarabine given during induction and two instead of three days of the anthracycline. Retaining cytarabine and daunorubicin and CPX-351 for use in consolidation has the major advantage of keeping

the active antileukemia therapies restricted to cytarabine and daunorubicin in both arms allows a better test of the hypothesis that ratiometric dosing explains the difference in observed efficacy and safety.

For patients at high risk of relapse (e.g. those with high-risk cytogenetics, antecedent hematologic disorder, or therapy-related AML), allogeneic stem cell transplantation (HSCT) is usually recommended if the patient is able to tolerate a transplant and has a suitable donor. This form of post remission therapy must be permitted for all patients on this study because its use as post remission therapy is associated with prolonged relapse free survival. Because of potential imbalances in use of HSCT, a formal sensitivity analysis will be performed in addition to an intent to treat analysis. The sensitivity analysis is performed by re-analyzing the data after censoring patients at the start of HSCT, so that survival potentially attributable to HSCT can be removed, isolating the contribution of study treatment.

Secondary AML is a term that has been used to cover a heterogeneous group of poor prognosis AML arising in a setting of prior treatment with cytotoxic agents or large field radiation therapy and/or antecedent hematologic disorders (AHD). At the chromosomal level, specific karyotypic abnormalities have been identified and linked to myelodysplasia. As a consequence, the term secondary AML is somewhat ambiguous and for the purposes of this trial, has been supplemented with specific WHO-based definitions of particular patient groups that have usually been grouped under the umbrella of secondary AML. This study is open to some but not all patient subsets grouped within secondary AML. Specifically included are patients with treatment-related AML, those with documented pre-existing myelodysplasia and CMMoL, and patients with de novo AML with specific chromosomal abnormalities linked to myelodysplasia per WHO criteria. Excluded are patients with MPN (except for CMMoL), MDS/MPN, and patients with multilineage dysplasia (per WHO) in the absence of a history of MDS or specific MDS-related cytogenetic abnormalities. The grounds for these exclusions are based on differences in the prognosis of these patient subsets, with low probability of response and poor survival among MPN and MDS/MPN patients and higher probability of response and survival among patients with multilineage dysplasia only. After excluding these patient subsets, the remaining patients still have high risk disease but have relatively similar prognosis. Patients eligible for this study continue to have poorer response rate, shorter duration of remission, and shorter overall survival than good risk de novo AML patients.¹³ If patient entry in the Phase II study in newly diagnosed patients (Study 204) is a guide to probable future patient accrual, the proportion of patients with high risk characteristics as defined above is 68/126 (54%) and after exclusion of patients with MPN or MDS/MPN is 58/126 patients (46%), suggesting that this study may access nearly half of all patients with AML in the 60-75 year age range and the majority (~65%) of patients with high risk AML.

Identifying patients with de novo AML eligible on the basis of cytogenetics will require waiting for the results of cytogenetics testing or performing a panel of FISH-based assays. Celator will make available a reference laboratory to perform cytogenetic assays with results available within 6 days; whereas local laboratories may require more time. It

is understood that rapid initiation of treatment is preferred and that delaying onset of treatment for 2-3 days beyond the initial work-up will be uncomfortable for patients and physicians alike. A review of the recent literature reveals that in a series of 1317 patients gathered from Cleveland Clinic and MD Anderson Hospitals¹⁴ longer time from diagnosis to treatment was not a significant factor in worsening rate of CR($p=0.63$) or reducing OS ($p=0.30$) in older patients. The authors concluded that delaying treatment did not seem harmful in older patients and patients may benefit from waiting for additional testing to return, allowing enrollment into studies that account for cytogenetic findings.

2.2 CombiPlex® Technology

In vitro studies have shown that antitumor activity can be enhanced when cytotoxic drugs are used in combination. This has led, over the years, to the use of drug combinations in the clinic such that cytotoxic drug combinations are now standard in many forms of cancer treatment. New anticancer drugs are typically first introduced in patients as single agents. After a maximum tolerated dose is determined for one agent, a second agent is added and the dose of one or both agents is adjusted on the basis of toxicity. The development of these combination regimens then is determined empirically on the basis of tolerability. However, in vitro, where the ratio of drugs used in combination can be controlled, it has been demonstrated that drug combinations providing synergy at one ratio may be simply additive or even antagonistic at other ratios.¹⁵ When individual free drugs are administered, each agent is handled differently by the body, resulting in varying distribution of the individual drugs to tumor sites which can result in drug ratios that are suboptimal or ineffective. Celator's technology is based on the findings that in vitro synergistic activity of antineoplastic drugs depends on specific drug ratios and that the in vivo activity of a combination depends on maintaining the synergistic ratio. In this way, the development of a particular chemotherapeutic regimen can be based on the most efficacious ratio rather than empirically based on toxicity.

The development of CPX-351 (cytarabine:daunorubicin) Liposome Injection was based on 1) defining a synergistic ratio of the two active moieties, cytarabine and daunorubicin, using cell-based screening assays and 2) designing a liposomal drug carrier to maintain this ratio after intravenous administration. This ratio was not based on the empirically-derived, toxicity-guided regimens currently used for cytarabine and anthracyclines.

2.3 Physical, Chemical and Pharmaceutical Information

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. These liposomes have a nominal diameter of approximately 100nm and are suspended in sucrose. Sterilization is achieved by filtration through a 0.22 μm filter.

CPX-351 is provided as a sterile, pyrogen-free lyophilized formulation in 50 mL glass, single-use vials. Each vial contains 100 units of CPX-351 where each unit contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes. The lyophilized cake is reconstituted with sterile water for injection to obtain a homogeneous dispersion at 5 units/mL. The composition of the formulation after reconstitution is listed in Table 1 below.

Table 1: Quantitative Composition

Component	mw	Amount per Vial	Amount per unit
Cytarabine, USP/PhEur	243	100 mg	1.0 mg
Daunorubicin HCl USP/ PhEur (reported as the free base)	528	44 mg	0.44 mg
Distearoylphosphatidylcholine	790	454 mg	4.5 mg
Distearoylphosphatidylglycerol	801	132 mg	1.3 mg
Cholesterol, HP	387	32 mg	0.3 mg
Copper gluconate, USP	454	92 mg	0.9 mg
Triethanolamine, NF	149	7 mg	0.07 mg
Sucrose, NF	342	2054 mg	20.54 mg

2.4 Product Label

CPX-351 (cytarabine:daunorubicin) LIPOSOME FOR INJECTION		100 units/Vial
Each unit contains 1.0 mg ($\pm 10\%$) Cytarabine and 0.44 mg ($\pm 10\%$) Daunorubicin (base) in liposomes containing DSPC, DSPG and cholesterol. Also contains copper as copper gluconate, triethanolamine and sucrose.		
Store refrigerated at 5°C ($\pm 3^\circ\text{C}$) in an upright position.		
FRAGILE: Do not drop		
Caution: New Drug – Limited by Federal Law to Investigational Use		
Manufactured for		
Celator Pharmaceuticals, Inc., [REDACTED]		
Lot # _____	Expiration Date: _____	

2.5 Pre-clinical Pharmacology & Toxicology

The pre-clinical pharmacology and toxicology are summarized in the Investigator's Brochure for CPX-351.

2.6 Brief Summary of Prior Clinical Studies

Three clinical studies have been completed with CPX-351 and a detailed presentation is available in the Investigator's Brochure. A brief summary of these studies is presented below.

2.6.1 Phase I Study of CPX-351: CLTR0305-101

The primary goal for this study was to establish the MTD for CPX-351 and recommend a dose for further study in a Phase II setting. Pharmacokinetic assessments were made at every dose level and patients were monitored for signs of antileukemic activity.

The dosage regimen was designed to mimic the 7-day drug exposure provided by conventional 7+3 treatment using a single induction course administering doses on Days 1, 3, and 5, by 90 minute infusion. Patients with AML (multiply relapsed, refractory, or with first CR duration of 6 months or less), ALL, and high risk MDS were eligible.

Dose limiting toxicities were observed at the 10th dose level: 134 u/m² (134 mg/m² cytarabine + 59 mg/m² daunorubicin). One patient had significant reduction in post treatment LVEF and as a result the Phase II studies included a cap (500 mg/m²) on cumulative anthracycline dose after one induction course of CPX-351 and patients with significant pre-existing cardiac disease were excluded. Other dose-limiting toxicities included hypertensive crisis and prolonged (>56 days) cytopenias.

The Phase I study of CPX-351 assessed the concentrations of cytarabine, daunorubicin, uracil arabinoside, and daunorubicinol at multiple dose levels and found that they exhibited mono-exponential, first order elimination with minimal early phase distribution.

The day 1 (single dose) and day 5 (multiple dose) C_{max} and AUC_(0-τ) were linear and the 5:1 molar ratio of cytarabine to daunorubicin was maintained for up to 24 hours after dosing at all dose levels on days 1 and 5.

CPX-351 was found to have markedly prolonged mean half life for both cytarabine and daunorubicin, greater drug exposure (AUC), and higher peak plasma concentrations (C_{max}). Measurable drug levels were present seven days after the last infusion of CPX-351 (Study Day 12).

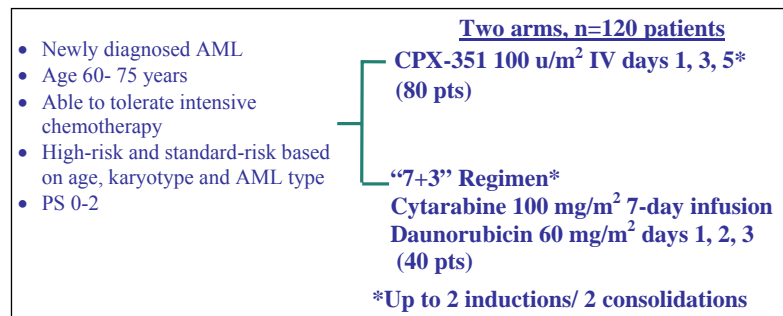
Response was observed in 1 of 3 multiply relapsed ALL and 10 of 43 AML patients. This was notable because most of the AML patients had already received cytarabine and daunorubicin in the past.

The maximally tolerated dose (101 u/m²) was defined and persistence of the 5:1 molar ratio for up to 24 hours in the plasma was confirmed. Multiple responses in previously treated AML patients confirmed antileukemic activity.

2.6.2 Phase II Study of CPX-351: CLTR0308-204

The 204 study was designed as a randomized study comparing CPX-351 head-to-head against 7+3, in newly diagnosed, older (age 60-75) patients with AML. The comparison of encapsulated cytarabine and daunorubicin (CPX-351) versus free cytarabine and daunorubicin (7+3) would be fully interpretable for relative efficacy and safety. One hundred twenty-seven patients were randomized 2:1 to receive CPX-351 or 7+3.

Response rate (CR+CRi) was the primary endpoint and superior response with a one-sided p-value of <0.1 was deemed sufficient for moving forward in development. Secondary endpoints were overall survival, event-free survival, CR+CRi duration, % leukemia-free after induction, safety and practicality of CPX-351 as consolidation therapy and the response rate of CPX-351 between de novo and secondary AML.



At entry patients were stratified by age (60-69 vs. 70-75), cytogenetics (< or ≥3 cytogenetic abnormalities), and type of AML (de novo vs. secondary). High risk patients were older (age 70 to <76) or had complex cytogenetics (≥3 cytogenetic abnormalities) or had secondary AML. Standard risk patients were younger (age 60-69), had non-complex cytogenetics (<3 abnormalities) and had de novo AML. After accrual was complete, [REDACTED] reviewed all of the cytogenetic reports and confirmed/corrected assignment of patients to <3 or ≥3 cytogenetic abnormalities and provided assessment of favorable, intermediate, and adverse cytogenetics per NCCN guidelines. Randomization and stratification were successful in balancing demographic and leukemia associated risk factors between the two study arms.

CPX-351 produced superior rates of leukemic-free state and response with similar duration of remission. It was notable that the improvement in response occurred predominately in the form of CRi (CR with incomplete hematologic recovery).

The study met the primary endpoint with a response rate of 66.7% compared to 51.2% with a p-value of 0.0712. Further analysis of response according to the stratification factors demonstrated consistent benefit for CPX-351 in response rate across every subgroup.

Kaplan-Meier (K-M) analysis after a minimum follow up of 1-year demonstrated non-significant improvements for CPX-351 for Event Free Survival (EFS) and Overall Survival (OS) in the overall population and the high risk strata.

Induction mortality was assessed at Day 30 and 60. A lower rate of early mortality was observed for CPX-351 treated patients at 60 days (4/85, 4.7% vs. 6/41, 14.6%, p=0.053). This result is the best evidence that CPX-351 treatment is acceptably safe and suggests that rapid clearance of leukemia may assist in reducing the early death rate.

CPX-351 treatment was associated with greater myelosuppression and more prolonged cytopenias, higher frequency of febrile neutropenia (63.5% vs. 51.2%), infections (e.g. bacteremia (42.4% vs. 22%)), and bleeding events (e.g. epistaxis (36.5% vs. 19.5%)). Otherwise, adverse events were qualitatively similar between both study arms. The lower mortality rate at 30 and 60 days indicates that CPX-351 was safe in spite of the consequences of greater myelosuppression.

Observations of reduced early mortality and a significant survival advantage (HR=0.41, p=0.02) among secondary AML patients suggest that clinical benefit is likely for this patient group in Phase III.

2.6.3 Phase II Study of CPX-351: CLTR0308-205

This study compared CPX-351 (100u/m²; Day 1, 3, 5) with salvage therapy in first relapse AML patients. This trial planned to accrue 120 patients with a 2:1 randomization to CPX-351 or investigator's choice of first salvage treatment. Responding patients were expected to receive allogeneic stem cell transplant for consolidation if donors were available. The European Prognostic Index was used to stratify patients. The primary endpoint was survival at one year, which was expected to be approximately 30% based on the literature. Secondary endpoints were CR+CRi rate, remission duration, event-free survival and 30/60/90 day mortality.

CPX-351 was able to increase the rate of leukemia-free state (77% vs. 60%), CR + CRi rate (49% vs. 41%), and had comparable 60-day mortality (15% vs. 16%), and better 90-day mortality (19% vs. 30%). After 1-year of follow up there were trends favoring CPX-351 for event free survival (HR=0.66, p=0.08) and overall survival (HR=0.75, p=0.19) among all patients and a subset analysis of the unfavorable risk group by European Prognostic Index showed a significant improvement in overall survival (HR=0.55, p=0.02). The proportion of CPX-351 patients alive at 1-year was 37% vs. 30% for control, and the proportion of unfavorable risk patients alive was 30% vs. 10%. These results in younger (age 18-65) patients with first relapse AML demonstrate potential efficacy among all patient subgroups with the largest improvement noted among higher risk patients and are entirely consistent with the results from newly diagnosed older patients in Study 204.

In summary, data from the Phase I and both randomized Phase II studies demonstrate consistent high level activity in AML marked by measurable increases in leukemia-free state and clinical response (CR + CRi) in most risk groups when compared to conventional therapy. The greatest relative difference occurred in the highest risk groups in both Phase II studies. The accumulated data suggest that CPX-351 may be a suitable replacement for the 7+3 regimen as first-line treatment and may be a useful alternative to current salvage regimens in the second-line setting. The proposed Phase III study is designed to confirm improved survival in newly diagnosed AML patients at high risk of poor outcome because of antecedent hematologic disorder (e.g. MDS and CMML), prior cytotoxic treatment (T-AML), and chromosomal abnormalities specifically linked to myelodysplasia (per WHO criteria) in patients with apparently de novo AML.

2.6.4 Copper Background

Copper is an essential element that is a component of a number of metalloenzymes acting as oxidases (e.g. diamine oxidase, monoamine oxidase, cytochrome c oxidase). The median absorption of copper from food (by an American adult) is 1.0 to 1.6 mg/day. The

tolerable Upper Intake Level for adults is 10 mg/day. A CPX-351 dose of 100 u/m^2 , would administer 36 mg of elemental copper to a patient with a BSA of 2.0 m^2 . Animal toxicology data suggest that elevated copper levels generally returned to baseline 1 to 2 weeks after the last dose. No toxicity was seen in animal studies attributable to copper. The data from the clinical studies are consistent with the preclinical findings. Since CPX-351 contains copper (0.18 mg copper per unit, in the form of copper gluconate), serum total copper levels were monitored in the Phase I clinical study.

Copper levels in patients receiving 3 doses of CPX-351 at 101 u/m^2 were elevated on day 7 (2 days after the last dose) but returned to normal levels in most patients by day 14. All patients had serum copper levels in the normal range by day 42 after induction. No acute toxicities attributable to copper exposure were observed.

The lack of toxicity observed in animal studies and in clinical studies to date is attributed to two factors: (1) most of the copper administered remains encapsulated within the liposome for most of the time it is in circulation limiting bioavailability and (2) the probability of copper-related toxicity is a function of C (the exposure to bioavailable copper) x T (the duration of exposure). If the exposure to elevated copper levels is limited to a few weeks, the risk of acute toxicity is probably low. Copper handling diseases generally require years of exposure to elevated copper levels before the onset of symptoms.

In this trial, serum copper levels will be monitored until return to baseline ($\pm 20\%$). Copper elimination after CPX-351 is likely via biliary excretion and elimination in the feces. It is expected that eligible patients with relatively normal liver function and unobstructed biliary systems should be able to eliminate the copper administered within a few weeks. Liver function tests will be performed regularly to assess hepatic dysfunction, a common manifestation of copper-related toxicity.

3.0 Study Objectives and Rationale

3.1 Primary Objectives

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 yrs) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.
- To confirm the safety of CPX-351

3.2 Secondary Objectives

- To confirm the improvement in rate of leukemia-free state, response (CR+CRi) rate, remission duration (relapse-free survival), event-free survival and overall best response (CR+CRi) rate following CPX-351
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients

- To assess and compare Pharmacoeconomic differences between CPX-351 and control

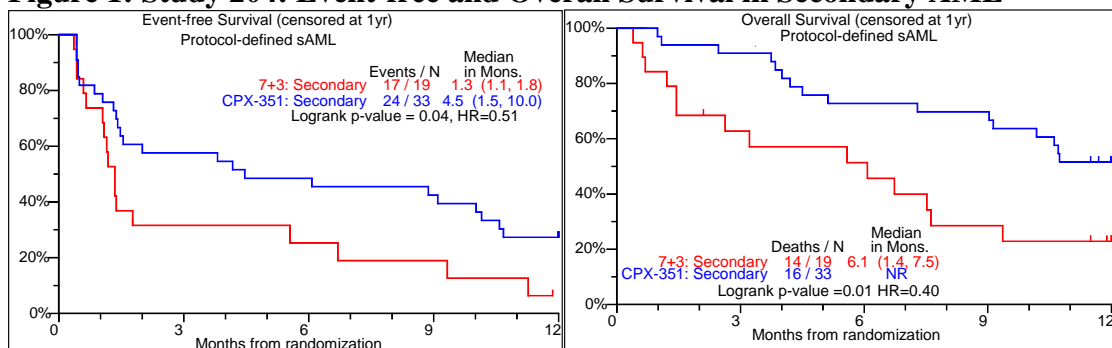
3.3 Study Rationale

The Phase I study demonstrated that an MTD in leukemia patients could be established for CPX-351 and that the intended 5:1 molar ratio of cytarabine to daunorubicin was maintained across multiple dose levels with markedly prolonged plasma half life of cytarabine and daunorubicin. At the MTD, CPX-351 was detectable in plasma at least 7 days after the last dose (Study Day 12). A substantial number of responses were observed in a population of patients with relapsed and refractory acute leukemia. This was notable because the majority had already received cytarabine and daunorubicin in the past. Data from this study was sufficient to give rise to two randomized Phase II trials, the first in newly diagnosed elderly AML patients (Study 204) and the second in first relapse patients age 18-65 (Study 205). Data from Study 204 provides the clinical rationale for this Phase III study.

Study 204 demonstrated consistent improvement in achievement of leukemia-free state and response (CR+CRi) across every AML subgroup studied. This included standard risk and high risk patients and within every constituent of the high risk group (age ≥ 70 , adverse cytogenetics, and secondary AML). Patient numbers were small in most subgroups, but the consistency of the response data is fairly persuasive that response differentials observed favoring CPX-351 are likely real.

As with response, CPX-351 appeared to improve event free survival across multiple subgroups although none were statistically significant. Analyses of the secondary AML subset indicated that this group of patients did particularly well relative to control by all efficacy and safety parameters. There were 52 patients with secondary AML by history, 33 randomized to CPX-351 and 19 randomized to 7+3. CPX-351 was superior for inducing a leukemia-free state (81.3% vs. 57.9%) and CR+CRi rate (57.6% vs. 31.6%), K-M analysis of event-free survival after 12 months minimum follow-up showed a significant difference in the CPX-351 arm (HR=0.51, p=0.04) and a significant difference in overall survival (HR=0.40, p=0.01).

Figure 1: Study 204: Event-free and Overall Survival in Secondary AML



When 30-day and 60-day mortality rates are assessed, CPX-351 is superior at 30-days (3.1% vs. 15.8%) and 60-days (6.1% vs. 31.6%) providing very strong evidence of acceptable safety in this higher risk subgroup.

The unexpected survival advantage in small numbers of secondary AML patients suggest a potential clinical benefit in this particular subgroup of patients that has traditionally had poor outcome after conventional intensive treatment with median survival duration of approximately 6 months. The study hypothesis is that CPX-351 will improve overall survival in newly diagnosed patients with selected antecedent hematologic disorders transformed to AML and in de novo AML patients with specific chromosomal abnormalities linked with myelodysplasia when compared to conventional 7+3 treatment.

4.0 Study Design

This study is a randomized, open-label, parallel-arm, standard therapy-controlled Phase III trial in patients with selected antecedent hematologic disorders transformed to AML (t-AML, MDSAML, and CMMoL AML (with documented history of MDS or CMMoL prior to transformation) and de novo AML with karyotypic changes characteristic of myelodysplasia, per WHO). Study enrollment duration is expected to be approximately 20 months. On entry, patients are randomized to receive either CPX-351 or standard induction treatment with cytarabine and daunorubicin (7+3 regimen). Patients are stratified to balance the likelihood of response and survival between the two arms. The study is designed in 2 phases; the Treatment Phase where patients receive up to two induction and two consolidation courses and are intensively monitored for safety (early deaths, adverse events, metabolic changes, etc.) and secondary efficacy endpoints (CR+CRi rate, rate of HSCT) and a Follow-up Phase, which begins 30-days after the last induction or consolidation course and continues for up to 5 years from randomization where patients are monitored for the primary (survival) and additional efficacy outcomes (event-free survival, best response and response duration). In addition, pharmacokinetic samples, at prespecified timepoints, will be collected from every patient.

4.1 Stratification

Patients are stratified to balance these prognostic factors across treatment arms.

Table 2 Definition of Strata:

Factor	Strata
Age	60-69 vs. 70-75
AML type	Treatment-related AML MDSAML with documented history of MDS <u>with</u> prior treatment with hypomethylating agents MDSAML with documented history of MDS <u>without</u> prior treatment with hypomethylating agents denovo AML with karyotype characteristic of MDS CMMoL AML with documented history of CMMoL

4.2 Patient Recruitment

All patients will be screened by a principal investigator or sub-investigator prior to entry on the study. An explanation of the study and discussion of the expected risks and benefits will be fully discussed with patients prior to the screening process in order for the patient to provide a voluntary written informed consent. Only eligible and consenting patients will be entered into the study.

At screening and prior to obtaining informed consent all prospective patients with newly diagnosed AML will have a detailed history of possible exposure to cytotoxic chemotherapy and radiation therapy. Documentation of prior cytotoxic therapy will be obtained from discharge summaries, pharmacy records, radiation therapy treatment records, etc. Patients with a history of MDS or CMMoL that has transformed to AML will also have documentation (specifically bone marrow examination records) obtained confirming the diagnosis and its prior treatment. Patients with prior treatment are eligible but are substratified based on prior treatment with a hypomethylating agent for MDS. Finally, patients with apparent de novo AML may still be eligible if they have specific chromosomal abnormalities linked to MDS (e.g. complex cytogenetics, -7, -5, etc. See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸).

4.3 Registration/Randomization Procedures

After providing informed consent, eligible patients are registered by providing the following to the sponsor prior to randomization:

Table 3: Documents Required for Registering a Patient

Patient with a history of:	Required Documentation
MDS/CMMoL	<ul style="list-style-type: none"> Bone marrow biopsy/aspirate report, including peripheral blood smear, documenting MDS/CMMoL diagnosis in the past
Cytotoxic Chemotherapy	<ul style="list-style-type: none"> Medical records documenting prior chemotherapy and the condition being treated Chemotherapy administration records (preferred) Pharmacy records Other direct evidence of chemotherapy administration
Ionizing Radiotherapy	<ul style="list-style-type: none"> Medical records documenting prior radiation therapy, including the size of the radiation field, the total dose, and the condition being treated Other direct evidence of radiation therapy administration
Apparent de novo AML	<ul style="list-style-type: none"> FISH or cytogenetics assay documenting karyotypic abnormalities characteristic of myelodysplasia. Documentation of qualifying cytogenetic abnormality must be available prior to registering the patient.

Prior to randomization the sponsor must review the documentation and approve the patient to be randomized onto the study. The randomization is done via a telephonic or internet-based interactive randomization system. Specific details and procedures will be provided under separate cover. The system will request information on the patient's age, AML history, MDS/CMMoL history and chemotherapy/radiation history, as well as cytogenetics and will confirm eligibility. After randomization, investigators are provided, in writing, the patient number and treatment assignment. The patients pharmacokinetic schedule assignment will also be provided. The patient number is used on all documentation and correspondence.

The following information will be required for patient randomization:

- Treatment center and investigator information
- Patient's initials and date of birth
- Cytogenetics (specific karyotype if it is the sole basis of eligibility or unknown)
- Disease history: MDS/CMMoL documentation and/or chemotherapy/radiation documentation

4.4 Patient Sample Size

Two-hundred forty (240) patients will be randomized to obtain approximately 220 evaluable patients. Equal numbers of patients will be randomized to CPX-351 (Arm A) or cytarabine and daunorubicin (Arm B, 7+3).

4.5 Induction

The initial induction course will begin within 24 hours of randomization. Following randomization, patients are monitored closely for response and safety. Depending on the type and extent of response as well as toxicity, the patient may continue on to consolidation therapy, receive a second induction, or be discontinued from the Treatment Phase and monitored in the Follow-up Phase.

Dosing for first induction:

- For **ARM A**: CPX-351 at 100u/m^2 will be administered on study days 1, 3 and 5
- For **ARM B**: 7+3: Cytarabine at a dose of $100\text{ mg/m}^2/\text{day}$ will be administered on study days 1-7 via continuous infusion and daunorubicin at a dose of $60\text{ mg/m}^2/\text{day}$ will be administered on days 1, 2 and 3.

4.6 Repeat of Induction

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving >50% reduction in % blasts count on the Day 14 bone marrow assessment. In case the Day 14 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-10 days later, at the discretion of the treating physician, in order to determine effect and need for second induction. Patients who are not expected to receive second inductions include all patients with evidence of aplasia/hypoplasia (<5% blast count) and patients with equivocal bone marrow results who will have marrow exam repeated. Patients unable to achieve a response (CR+CRi) after two inductions are discontinued from the treatment period and followed for survival.

Dosing for second induction:

- For **ARM A**: CPX-351 at 100 u/m^2 will be administered on days 1 and 3
- For **ARM B**: Cytarabine at a dose of $100\text{ mg/m}^2/\text{day}$ will be administered on days 1-5 and daunorubicin at dose of 60 mg/m^2 will be administered on days 1 and 2 (5+2)
- The second induction must be started by Day 35.

4.7 Consolidation Therapy

Post-remission therapy in older patients with AML produces modest improvement in patient outcomes and should be extended to as many patients as possible. Only patients with documented response (CR or CRi) are eligible for consolidation. The bone marrow aspirate/biopsy report and peripheral blood count data is to be made available to the sponsor before beginning consolidation. Prior to the first consolidation the patients LVEF must be documented to be $\geq 50\%$ and prior to every consolidation the patients must have a PS of 0-2. First consolidation must be given no earlier than 35 days after the start of the last induction and no later than 75 days after the start of the last induction. Patients must have recovered to ANC $>500/\mu\text{L}$ and platelets $>50,000/\mu\text{L}$ to be eligible for first or second consolidation. The second consolidation is administered 35-56 days after the start of the first consolidation.

Dosing for consolidation:

- For **ARM A**: CPX-351 at 65 u/m^2 will be administered on days 1 and 3
- For **ARM B**: Cytarabine at a dose of $100 \text{ mg/m}^2/\text{day}$ will be administered on days 1-5 and daunorubicin at dose of 60 mg/m^2 will be administered on days 1 and 2 (5+2)

No other chemotherapy consolidation treatment is permitted. Only HSCT is permitted in place of, or following, chemotherapy consolidation.

4.8 Salvage Therapy

Patients who never achieve CR/CRi following initial induction and patients who achieve CR/CRi and later relapse may receive salvage therapy.

4.9 Follow-up Phase

The Follow-up Phase consists of routine visits or other patient contact to assess for the primary endpoint (survival) and other time to event endpoints (time to relapse). Patients enter the follow-up phase at different times depending on their treatment response. See Table 4:

Table 4: Follow-up Phase

CR	Begins after peripheral blood count recovery following the last course of treatment (Induction and/or Consolidations)
CRi	Begins after peripheral blood counts recover (to at least ANC to $\geq 500/\mu\text{L}$ <u>and</u> platelets to $\geq 50,000/\mu\text{L}$) or stabilize after the last course of treatment (Induction and/or Consolidations)
PD/treatment failure	Begins 30 days after documentation of persistent AML or discontinuation from study therapy if no benefit from further protocol-defined therapy is expected. The 30-day period is to document recovery from acute AEs
Adverse Event	Begins 30 days after an AE which, in the opinion of the investigator, requires discontinuation of any further protocol therapy. The 30 days allows for documentation of recovery from the AE.

The follow-up period continues until the death of the patient and up to 5 years from randomization. Patients who complete the Treatment Phase with significant residual non-hematopoietic toxicity will be followed for up to 4 additional weeks until toxicity resolves to \leq grade 1, stabilizes or initiation of new therapy, whichever occurs first. Patients with unresolved AEs after 4 weeks will have the events classified as permanent sequelae.

Follow-up for CR duration, EFS and Adverse Events (if applicable) are discontinued at the time of relapse, start of salvage or non-protocol treatment for leukemia (for persistent disease). All patients who have persistent or relapsed disease or who are transferred for stem cell transplant will be followed for up to 5 years for relapse and survival.

4.10 Study Modification/Discontinuation

Any modifications to the study will be documented in a revised protocol with a new assigned version. The revised protocol will have an appendix which will detail the revisions to the document.

The Sponsor may stop the trial early for the following reasons:

- Unacceptable toxicity
- Discontinuation of drug development
- Poor enrollment
- Request by a regulatory authority

In the case of study discontinuation, all participating institutions will be notified with procedures for discontinuing patients from the trial and informing the EC/IRBs (See Section 12.5).

4.11 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will periodically monitor the ongoing study for safety and efficacy considerations. The DSMB will consist of independent reviewers who are not directly involved in the conduct of the study and will advise the Sponsor of any trends or safety issues which may impact the study and/or the study patients. The DSMB will operate according to a charter which will be reviewed and ratified before the initiation of the study. The DSMB, at a minimum, will:

- Consist of at least 2 hematologists + 1 cardiologist + 1 statistician
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and at end of study to review day 60 deaths and SAEs
- Conduct a single interim analysis after 60 patients (30 per arm) have been evaluated for induction mortality with early stop rules. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB.

4.12 Central Review of Diagnosis and Response:

Participating centers are required to provide documentation of each patient's antecedent hematologic disorder or prior cytotoxic treatment before randomization (see Section 4.3).

Every attempt will be made to confirm eligibility at time of randomization. After randomization, this documentation will be independently reviewed and the diagnosis confirmed. If there is doubt about the diagnosis of t-AML, MDS-AML or CMMoL-AML during the process of independent review, additional materials will be requested and reviewed. The specific requirements for diagnosis and details of the process for review and confirmation of diagnosis will be detailed in a separate operating plan.

In addition, an independent review of hematopathology and peripheral blood reports will be done to document response (CR+CRi) to therapy. A charter will be reviewed and ratified prior to the initiation of the study. The central reviewer will also be a non-voting member of the DSMB, providing the committee with progress reports on the quality of diagnostic and response documentation.

5.0 Selection and Withdrawal of Patients

5.1 Study Population

5.1.1 Inclusion criteria

- 5.1.1.1 Ability to understand and voluntarily sign an informed consent form
- 5.1.1.2 Age 60-75 years at the time of diagnosis of AML
- 5.1.1.3 Pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow)
- 5.1.1.4 Documentation of Antecedent Hematologic Disorder:
 - Therapy-related AML: Documentation of prior cytotoxic therapy or radiation therapy for an unrelated disease in a discharge summary or pharmacy records or radiation therapy records
 - MDS-AML: Bone marrow documentation of MDS prior to diagnosis of AML
 - CMMoL-AML: Bone marrow documentation of CMMoL prior to diagnosis of AML
 - *de novo*-AML with FISH or cytogenetic changes linked to MDS per WHO criteria (see APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸)
- 5.1.1.5 Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- 5.1.1.6 Able to adhere to the study visit schedule and other protocol requirements
- 5.1.1.7 Laboratory values fulfilling the following:
 - Serum creatinine < 2.0 mg/dL
 - Serum total bilirubin < 2.0 mg/dL, patients with Gilbert's Syndrome should contact the medical monitor
 - Serum alanine aminotransferase or aspartate aminotransferase < 3 times the ULN. Note: If elevated liver enzymes are related to disease; contact medical monitor to discuss.
- 5.1.1.8 Cardiac ejection fraction \geq 50% by echocardiography or MUGA

- 5.1.1.9 Patients with second malignancies in remission may be eligible if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic chemotherapy, documented by imaging, tumor marker studies, etc., at screening. Patients maintained on long-term non-chemotherapy treatment, e.g., hormonal therapy, are eligible.

5.1.2 Exclusion Criteria

- 5.1.2.1 Patients with history of myeloproliferative neoplasms (MPN) (defined as a history of essential thrombocythosis or polycythemia vera, or idiopathic myelofibrosis prior to the diagnosis of AML) or combined MDS/MPN are not eligible.
- 5.1.2.2 Acute promyelocytic leukemia [t(15;17)] or favorable cytogenetics, including t(8;21) or inv 16 if known at the time of randomization.
- 5.1.2.3 Clinical evidence of active CNS leukemia
- 5.1.2.4 Patients with active (uncontrolled, metastatic) second malignancies are excluded.
- 5.1.2.5 Prior treatment intended for induction therapy of AML; only hydroxyurea is permitted for control of blood counts. For example, a patient with MDS that changes HMA dose and schedule after the diagnosis of AML is excluded. AML-type therapy, such as cytarabine alone ($>1\text{g}/\text{m}^2/\text{day}$) or cytarabine plus an anthracycline as well as prior HSCT are also excluded.
- 5.1.2.6 Administration of any therapy for MDS (conventional or investigational) must be completed by 2 weeks of the first dose of study drug; in the event of rapidly proliferative disease use of hydroxyurea is permitted until 24 hours before the start of study treatment. Toxicities associated with prior MDS therapy must have recovered to grade 1 or less prior to start of treatment.
- 5.1.2.7 Any major surgery or radiation therapy within four weeks
- 5.1.2.8 Patients with prior cumulative anthracycline exposure of greater than $368\text{mg}/\text{m}^2$ daunorubicin (or equivalent), see APPENDIX 8: Anthracyclines Equivalents Guidelines
- 5.1.2.9 Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent
- 5.1.2.10 Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)
- 5.1.2.11 Active or uncontrolled infection; patients with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥ 72 hrs.
- 5.1.2.12 Current evidence of invasive fungal infection (blood or tissue culture); patients with recent fungal infection must have a subsequent negative cultures

to be eligible; known HIV (new testing not required) or evidence of active hepatitis B or C infection (with rising transaminase values)

5.1.2.13 Hypersensitivity to cytarabine, daunorubicin or liposomal products

5.1.2.14 History of Wilson's disease or other copper-metabolism disorder

5.2 Withdrawal of Patients

Patients will be discontinued from the Treatment Phase and enter the Follow-up Phase for assessment of efficacy endpoints under the following circumstances:

- Completion of Treatment Phase
- Persistent disease: lack of a response to treatment
- Relapsed disease: re-appearance of disease following CR or CRi
- Unacceptable toxicity
- Patient non-compliance with protocol
- Administration of non-protocol chemotherapy
- Intercurrent illness which, in the judgment of the investigator, affects assessment of clinical status to a significant degree, and requires discontinuation of protocol therapy.

During any phase of the study, if a patient requests to stop treatment and/or follow-up, the patient will be discontinued and no further information will be collected. The patient will be classified as withdrawal of consent. Any patient that dies on or before Day 7 will be replaced.

6.0 Treatment of Patients

See APPENDIX 1: Patient Evaluation Flow Sheet

6.1 Pre-Treatment Evaluations

After providing informed consent, eligible patients are registered by providing documentation of high-risk (secondary) AML to the sponsor PRIOR to randomization. The list of required documents can be found in Section 4.3 on page 25.

The date of the first test or exam will be considered as the date of the screening visit.

Procedure	Evaluation	Timing
Informed Consent	It should be personally signed and dated by the patient. The responsible investigator must also personally sign and date the document. A copy of the Informed Consent must be given to the patient. The patient's study screening must be conspicuously noted in the source documentation.	Informed consent should be obtained prior to initiation of screening procedures. If the period between ICF signature date and screening visit is ≥ 30 days the patient must sign another ICF.
Demography	date of birth, sex, race, ethnicity	Within 14 days prior to randomization

Procedure	Evaluation	Timing
Medical History	Complete medical history <ul style="list-style-type: none"> Resolved conditions Intermittent conditions Concurrent illnesses Previous surgeries 	Within 14 days prior to randomization
Leukemia History	<ul style="list-style-type: none"> Leukemia, MDS, CMMoL History Prior chemotherapies Prior hypomethylating agents 	Within 14 days prior to randomization
Physical Exam	Objective review of body systems Height Weight BSA ECOG Performance Status	Within 3 days prior to randomization
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Within 3 days prior to randomization
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Within 1 day prior to randomization
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Within 1 day prior to randomization
Copper levels	Serum copper (performed by a central laboratory)	Within 3 days prior to randomization
Urinalysis	pH specific gravity glucose protein ketones blood	Within 3 days prior to randomization
Bone Marrow Aspiration/Biopsy	Morphology	Within 14 days prior to randomization
Diagnostic Imaging	Chest X-ray or Chest CT Echocardiography or MUGA scan (sent to a central laboratory)	Within 28 days prior to randomization
ECG		Within 14 days prior to randomization
Cytogenetics	Cytogenetics (performed locally)	Within 3 months prior to randomization: patients may be randomized and treated prior to the

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Procedure	Evaluation	Timing
	Cytogenetics (performed by a central laboratory): For those centers that have a turn-around of 7 or more days, a central laboratory will be made available to screen de novo patients for eligible karyotypes (See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia ¹⁸ . A separate informed consent form is used to screen de novo patients for eligible karyotypes with a short eligibility checklist. See Section 9.4.3.	cytogenetic test results; however, every attempt should be made to have the results prior to randomization
Molecular Studies	Central laboratory evaluation of CEBPA, FLT3, and NPM1	Within 3 months prior to randomization: patients may be randomized and treated prior to receiving the results of molecular tests

6.2 Evaluation during Treatment Phase

Inductions and consolidations are administered as courses. A course consists of the administration of therapy with scheduled assessments to evaluate the response to treatment. The first induction may end before the completion of all evaluations if a second induction is necessary, (see Section 4.6). Induction is completed when a patient has

- A confirmed CR (see section 8.4)
- A CRi (see section 8.4) and is to begin consolidation treatment before hematologic count recovery
- Persistent/recurrent disease (PD/relapse)
- Response evaluation cannot be performed because of the patient's condition and no further study treatment can or will be administered.

Patients with a CR or CRi may receive up to two consolidation treatments. Evaluations on Days 1-7 must be performed on the day indicated; all other evaluations are to be performed on the Study Day indicated plus or minus 2 days. Each course requires the following evaluations:

Procedure	Evaluation	Timing
Physical Exam	Objective review of body systems Weight BSA	Days 14 and 42
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Days 14 and 42
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Days 1, 3, 5, 7, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase

Procedure	Evaluation	Timing
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Days 1, 3, 5, 7, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase
PK sampling	Plasma concentrations for cytarabine and daunorubicin and metabolites (performed by bioanalytical laboratory)	CPX-351 patients will be sub-randomized to one of two PK sampling schedules: <u>Schedule 1:</u> Day 1: 45 min, 3 hrs, 8 hrs, prior to dosing on Day 3 (48 hrs (+/- 6 hrs)) or <u>Schedule 2:</u> Day 1: End of Infusion, 2 hrs, 6 hrs, prior to dosing on Day 5 (96 hr (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF. Four samples are collected from each patient randomized to CPX-351.
Copper levels	Serum Copper (performed by a central laboratory)	After the last induction that the patient receives; See Section 9.4.1 for details
Bone Marrow Evaluation	Morphology	Required at Day 14-21 after every induction; Required at recovery to confirm response (CR/CRi) or persistent disease; in case Day 14-21 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine antileukemic effect and need for second induction.
Cytogenetics Molecular Studies	Cytogenetics (performed locally) Molecular Studies (performed by a central laboratory)	Required in patients with a CR or CRi with positive baseline findings (perform at the time of bone marrow assessment for CR or CRi). Optional in patient with normal findings at baseline
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	After the last induction that the patient receives; See Section 9.3 for details
Response Assessment		See Section 8.4.1
Adverse Events/Toxicity	CTCAE v.3 assessment	Continual assessment starting from the first dose until 30 days after completion of the Treatment Period.
Concomitant Medications	GCSF Anti-infectives	Continually assess during Treatment Period

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6.3 Day 150 Evaluations

All patients randomized to this protocol must have the following assessments performed 150 (± 10) days from randomization or 45 days after the last treatment, whichever is later. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or if they have been transferred for HSCT.

	Evaluation	Timing
ECG		Day 150 ± 10 days
Copper levels	Serum Copper (performed by a central laboratory)	Day 150 ± 10 days See Section 9.4.1 for details
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	Day 150 ± 10 days See Section 9.3 for details

6.4 Early Termination or End of Treatment Phase

Any patient that completes or discontinues treatment must have the following evaluations performed within 30 days after termination and prior to the initiation of any salvage therapy, if not performed within the last 30 days:

Procedure	Evaluation	Timing
Diagnostic Imaging	Echocardiography/MUGA	Within 30 days after discontinuation if a study has not been performed since last treatment or before the initiation of any non-protocol treatment
ECG		Within 30 days after discontinuation
Adverse Events/Toxicity	CTCAE v.3 assessment	Assess Adverse events that were ongoing at the time of discontinuation and record and report any new serious adverse events (up to 30 days after discontinuation)
Response Assessment	Best Response Reason for End of Treatment	

6.5 Evaluation during Follow-up Phase

The following evaluations are completed during the follow-up phase:

Procedure	Evaluation	Timing
Patient status report	Survival status	Once monthly until 1 year from randomization, after the first year record only the date of death or alive at Year 5 (Day 1825).
	Relapse status New anti-leukemic therapies	Once monthly until 1 year from randomization, after the first year record only the date of relapse and any new leukemic therapies.
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Once monthly until 1 year from randomization or the initiation of new therapy and/or relapse
Bone Marrow Evaluation	Morphology	For patients in CR or CRi <u>perform at any time that there is a suspicion of relapse.</u> For patients in CR, perform if peripheral blood counts fall below 1000/ μ L for ANC or 100,000/ μ L for platelets for >1 month or at any time there is suspicion of relapse. For patients in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a patient with a CRi recover to CR levels ($\geq 1000/\mu$ L for ANC or $\geq 100,000/\mu$ L for platelets), perform a bone marrow evaluation within 14 days to confirm CR. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following relapse.
Diagnostic Imaging	Echocardiography or MUGA	If last LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline or until 1 year from randomization. Persistent reductions in LVEF of >10% and failing below 50% lasting >1 year are considered permanent sequelae.
Biochemistry	BUN Creatinine Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT Protein Calcium Albumin Glucose	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from randomization, or the initiation of new therapy and/or relapse. (which ever is earliest)
Copper levels	Serum Copper (performed by a central laboratory)	If elevated copper (>20% above ULN) persists at Day 150 perform monthly until abnormality returns to baseline or until 1 year from randomization.

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Procedure	Evaluation	Timing
Adverse Events/Toxicity	CTCAE v.3 assessment	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.

7.0 Drug Administration

The responsibility for treatment of patients rests with the individual investigator. Protocol treatment must begin within 24 hours of randomization.

First Induction:

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	100u/m ² /day	IV	90 minutes*	Days 1, 3 and 5
B	Cytarabine	100mg/m ² /day	IV	7 days	Days 1-7 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1, 2 and 3

Second Induction:

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	100u/m ² /day	IV	90 minutes*	Days 1 and 3
B	Cytarabine	100mg/m ² /day	IV	7 days	Days 1-5 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1 and 2

Consolidations (up to two are permitted):

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	65u/m ² /day	IV	90 minutes*	Days 1 and 3
B	Cytarabine	100mg/m ² /day	IV	5 days	Days 1-5 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1 and 2

*Approximately

7.1 Drug Preparation and Administration

7.1.1 CPX-351

7.1.1.1 Drug Preparation

The appropriate number of vials of CPX-351 (cytarabine:daunorubicin) Liposome Injection should be removed from the refrigerator prior to reconstitution. Reconstitute with 19 mL of sterile water for injection using a 20 mL syringe. Do not heat CPX-351 (cytarabine:daunorubicin) Liposome Injection. After reconstitution, invert vials gently 3-4 times and let rest for 15 minutes and repeat vial inversion prior to withdrawing drug for dilution. The concentration of the reconstituted dispersion is 5 u/mL. CPX-351 (cytarabine:daunorubicin) Liposome Injection should be diluted in approximately 500 mL of sodium chloride injection or dextrose injection.

The IV bags and infusion sets must be non-DEHP. Aseptic technique must be strictly observed throughout the handling of CPX-351 (cytarabine:daunorubicin) Liposome Injection since no bacteriostatic agent or preservative is present. The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection must be started within 4 hours of dilution. Vials are for single use. Unused material should be recorded as such and

discarded according to institutional policies. Procedures for proper handling and disposal of anticancer drugs should be implemented.

7.1.1.2 Drug Administration

The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection will be performed through a central venous catheter, using an infusion pump to ensure that the drug is infused over the specified time period. Non-DEHP containing administration sets should be used. **Do not use an in-line filter.** CPX-351 should never be given by the intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes via an infusion pump. Flush the line to ensure administration of the full dose.

The dosage (total units and u/m^2), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

7.1.2 Cytarabine and Daunorubicin "7+3"

7.1.2.1 Control Arm Drug Sourcing:

The drug products that may be used for the control arm will be sourced by the investigational site. Cytarabine and daunorubicin are approved in the US, Canada and EU and will be obtained from the appropriate market (US for investigational sites in the US, Canadian for sites in Canada, EU country for sites in EU). If for any reason, drug supplies for cytarabine or daunorubicin are or might be unavailable or insufficient to complete a treatment cycle, contact the sponsor as soon as possible: Telephone: + [REDACTED] or fax: [REDACTED] or email: [REDACTED].

7.1.2.2 Cytarabine

Cytarabine is not provided as a study drug and must be supplied by the treating institution. Prepare and administer cytarabine according to institutional guidelines and the package insert. Below are general guidelines for preparation and administration.

The drug is available in vials of 100mg, 500mg, 1g and 2g – containing white lyophilized substance. The drug must be reconstituted prior to use.

A solution in which a slight haze develops should not be used, it should be discarded and another dose of the drug should be prepared. The ready solution should be stored at temperatures of 15-30°C. The solution should not be stored for prolonged periods of time and infusion should start as soon as feasible. All infusion solutions must be inspected visually for particulate matter and discoloration prior to administration. The dosage (total mg and mg/m^2), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

Cytarabine is administered as a 7 day (for first induction) or 5 day (for second induction or consolidations) continuous intravenous infusion.

7.1.2.3 Daunorubicin

Daunorubicin is not provided as a study drug and must be supplied by the treating institution. Prepare and administer daunorubicin according to institutional guideline and the package insert. Below are general guidelines for preparation and administration.

The drug is provided as the HCl salt in vials containing a reddish lyophilized powder which should be reconstituted for infusion. Vials of 20 mg and 50 mg are available. The smaller packaging vials contain the equivalent of 20mg daunorubicin base (21.4 daunorubicin HCl - lyophilized powder) and 100mg mannitol. Each 50 mg vial contains 53.5 mg daunorubicin hydrochloride, equivalent to 50 mg daunorubicin base, and 250 mg of mannitol. The contents of the 20 mg vial should be reconstituted with 4 mL of Sterile Water for Injection, USP, and agitated gently until the material has completely dissolved. The sterile vial contents provide 20 mg of daunorubicin, with 5 mg of daunorubicin per mL. The contents of the 50 mg vial should be reconstituted with 10 mL of Sterile Water for Injection, USP, and agitated gently until the material has completely dissolved. The sterile vial contents provide 50 mg of daunorubicin, with 5 mg of daunorubicin per mL. The reconstituted solution is stable for 24 hours at room temperature and 48 hours if refrigerated. The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP. Daunorubicin should not be administered mixed with other drugs or heparin. Store the unreconstituted powder according to label instructions at a controlled room temperature, 15-30°C (59-86°F). The dosage (total mg and mg/m²), start/stop time of the infusion, total volume infused, must all be documented in the patient's chart.

Daunorubicin Hydrochloride for Injection is administered intravenously into the tubing or sidearm in a rapidly flowing intravenous infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.

7.2 Drug Accountability

The study pharmacist or designee must maintain records of the delivery of CPX-351 to the study site, the inventory at the site, the use by each patient, and the disposition of unused product. These records should include dates, quantities, lot numbers, expiration dates and patient identifications. Institutions should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product received from the Sponsor. Records of storage conditions (temperature logs) must be kept for the entire period that CPX-351 is maintained at the institution.

7.3 Dose Reductions and Delays

It is the intention of the study to treat every patient at full dose. Doses may be delayed due to toxicities (for example hypersensitivity reactions). Any doses missed or delayed due to toxicity may be administered as soon as the patient has recovered from the toxicity. Investigators may contact the Medical Monitor to request delay or discontinuation of treatment if it is in the best interest of the patient. Toxicities will be

graded using the CTCAE Version 3.0 (See APPENDIX 5: Common Terminology Criteria for Adverse Events V3.0 (CTCAE)). Toxicities for cytarabine and daunorubicin are relatively well known, and are outlined in the product information for each of these drugs.

7.4 Concomitant Therapy

7.4.1 Premedication

7.4.1.1 CPX-351

Nausea and vomiting:

Patients may be premedicated for nausea and vomiting according to institutional standards.

Hypersensitivity/Infusion-related reactions:

Patients will not be routinely premedicated for hypersensitivity or infusion-related reactions initially during the first infusion of the first treatment course. If the patient develops a hypersensitivity reaction then he/she should be pre-medicated at all subsequent infusions.

Suggested guidelines for management of hypersensitivity reactions:

Mild symptoms (e.g., mild flushing, rash, pruritus):

Stop infusion and supervise at bedside with monitoring of vital signs

Reinitiate infusion slowly (halving the rate of infusion) +/- premedication

Moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort):

Stop infusion and give IV diphenhydramine, 20-25 mg (or equivalent) and IV dexamethasone 10 mg.

Do not reinitiate infusion. Premedicate on re-treatment. Retreat at same dose and rate.

Severe/life-threatening symptoms (e.g. hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria):

Stop infusion. Administer IV diphenhydramine and dexamethasone as indicated above.

Add epinephrine (adrenaline) or bronchodilators if indicated. Do not reinitiate infusion.

Do not retreat. Report as a serious adverse event.

If hypersensitivity or infusion-related reactions become a clinically relevant toxicity, then premedication for hypersensitivity reactions will be instituted with drugs, doses and schedule according to each investigator's preference. Additionally, a decision may be made to prolong the infusion time to two hours or more.

7.4.1.2 Daunorubicin and Cytarabine

Premedication for daunorubicin and cytarabine are provided according to institutional policy and procedure.

7.4.2 Permitted therapy

Patients may receive ongoing supportive and palliative care (e.g. pain control) as clinically indicated throughout the study.

Infection Prophylaxis: Prophylactic use of anti-infectives is highly recommended during the period of profound neutropenia until ANC returns to 500/ μ L or greater. The choice of anti-infectives will be according to institutional protocol. Use of anti-infective agents as prophylaxis and treatment must be documented on the case report forms.

Growth Factor support: The use of growth factors will be according to institutional protocol and according to ASCO criteria.¹⁶ Use of growth factors must be documented on the case report forms.

Transfusion support: The use of transfusion support (RBCs and platelets) will be according to institutional protocol. Use of transfusion support must be documented on the case report forms.

7.4.3 Therapy that is not permitted

Other anti-cancer treatment and other investigational therapy(ies) are not permitted during the Treatment Phase. In the event of persistent disease or relapse the patient may receive other anti-leukemic therapies and is followed for survival.

7.5 Duration of Protocol Treatment

Patients may continue on study provided they have not met the criteria for discontinuation of therapy (See Section 5.2). The table below summarizes the expected duration of the Treatment Phase. Patients may receive up to two induction courses followed by up to two consolidation courses. After the Treatment Phase, patients are followed for up to 5 years from the time of randomization.

No. of Courses (Inductions or Consolidations)	Duration of Treatment Phase	Duration of Entire study
1	~ 42-56 days	5 years
2	~ 84-112 days	5 years
3	~ 126-168 days	5 years
4	~ 168-224 days	5 years

8.0 Assessment of Efficacy

8.1 Evaluable for Efficacy

All analyses will be based on the intent-to-treat principle; all randomized patients are evaluable for efficacy. Patients that die on or before Day 7 will be replaced.

8.2 Overall Survival

All randomized patients are assessed for overall survival. Overall survival is measured from the date of randomization to death from any cause, patients not known to have died at last follow-up are censored on the date they were last known to be alive. Patients will be followed for up to 5 years. Overall survival will be analyzed on an intent-to-treat basis with all randomized patients analyzed. A sensitivity analysis will be performed in which patient receiving hematopoietic bone marrow transplant are censored for survival at the start of conditioning therapy, to eliminate transplant as a confounding factor in the analysis of overall survival. For more detail, see Section 11.5.5.

8.3 Event-free Survival

All randomized patients are assessed for Event-free survival. Event-free survival is defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi or death from any cause, whichever comes first. Patients alive and not known to have any of these events are censored on the date they were last examined.

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8.4 Response Assessment Criteria

During the Treatment Phase patients will be assessed for response according to the following criteria¹:

Complete remission (CR) ^a	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq 1.0 \times 10^9/L$ (1000/ μL); platelet count $\geq 100 \times 10^9/L$ (100,000/ μL); independence from red cell transfusions
CR with incomplete recovery (CRi) ^b	All CR criteria except for residual neutropenia ($< 1.0 \times 10^9/L$ [1000/ μL]) or thrombocytopenia ($< 100 \times 10^9/L$ [100,000/ μL])
Best Response	See Section 8.4.2
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia (blasts in peripheral blood, extramedullary leukemia, or persistence in the bone marrow)
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available at recovery
Relapse ^c	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

^aBone marrow assessment REQUIRED to confirm CR. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

^b Bone marrow assessment REQUIRED to confirm CRi. Some patients may not achieve complete hematologic recovery prior to initiation of consolidation. CRi cannot be declared earlier than Day 35 to allow adequate time for documentation of peripheral blood recovery. Consolidation may begin no earlier than 35 days after the last induction course.

^cIn cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

The response of patients with no post-baseline bone marrow assessment is entered as not done.

8.4.1 Timing of response assessment

In general, the patient's response to induction therapy is made on the first day when all criteria for CR or treatment failure are met. The bone marrow assessment and the peripheral counts are not required to be performed on the same day but recovery of counts (including absence of peripheral blasts) must be performed within 14 days of the bone marrow assessment. The timing of other outcomes is recorded as follows:

1. After one or two induction course(s), PD is declared on the day of the bone marrow showing persistent AML.
2. CRi is declared on or after Day 35 following the last induction course when the patient's bone marrow (performed between day 35-56) demonstrates absence of leukemia and the peripheral blood counts have partially recovered but appear stable (performed at least twice between day 35-56).
3. For patients with sufficient blood count recovery ($ANC \geq 500/\mu L$ and platelets $\geq 50,000/\mu L$) that consolidation therapy is planned, CRi is declared on the day consolidation therapy is initiated but the peripheral counts have not met the full CR criteria. Consolidation must begin after day 35.

8.4.2 Best Response

Patients who complete the induction(s) with a response of CRi may be upgraded to a CR during or after consolidation if the patient's peripheral blood counts meet the criteria for CR after declaration of a CRi. To upgrade a response to CR both peripheral blood and bone marrow assessment are not required on the same day but must be obtained within a 14 day period of each other and all criteria for CR must be met (within a 14 day period must have full recovery AND be leukemia-free).

8.5 Remission Duration

Only patients achieving CR or CRi are assessed for remission duration. Remission duration is measured from the date of achievement of a remission (CR/CRi) until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined. For patients whose best response is upgraded from CRi to CR, remission duration will be calculated from date of CRi to date of relapse or death.

8.6 Morphologic Leukemia-free State

All randomized patients that have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction are assessed for morphologic leukemia-free state. Morphologic leukemia-free state is defined as bone marrow blasts $< 5\%$ AND absence of Auer rods and/or extramedullary disease.¹

8.7 Stem Cell Transplant

The number and percentage of patients transferred for stem cell transplant will be quantitated and compared.

9.0 Assessment of Safety

9.1 Evaluable for Safety

All patients who have received at least one dose will be considered evaluable for safety.

9.2 Adverse Events

9.2.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An adverse event is considered serious if it meets any of the serious criteria listed in Section 9.2.2. To ensure no confusion or misunderstanding of the difference between the terms “serious” and “severe”, which are not synonymous, the following clarification is provided:

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Adverse events are to be recorded in the case report form from the start of the infusion on Day 1 to the last day of the treatment period, with the exception of serious adverse events. (See Section 9.2.2)

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An unexpected ADR is any adverse reaction not identified in nature or intensity in the current Investigator’s Brochure.

9.2.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any adverse event that at any dose:

Results in death (grade 5)
Is life-threatening
Requires inpatient hospitalization or prolongation of existing hospitalization
Results in persistent or significant disability or incapacity
Is a congenital anomaly/birth defect

These events are to be reported as serious from the start of the infusion on Day 1 to 30 days after completion of the treatment period. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate 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 or may require intervention to prevent one of the events listed above.

Exceptions to the definition of SAE are uncomplicated febrile neutropenia and grade 1-3 bleeding events (with or without platelet transfusions). These events, as they are common and expected in this patient population will NOT be reported as SAEs, but as AEs only. Hospitalizations for routine procedures, investigations and chemotherapy administration are NOT considered SAEs in this protocol.

9.2.3 Serious Adverse Event Reporting Instructions

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax within 24 hours to the Sponsor or its designee. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information is sent to the Sponsor or its designee via the original Serious Adverse Event Form, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

The telephone and fax numbers of the local Clinical Research contact person and the contact person in the local department of Clinical Safety, specific to the site, must be listed in the investigator folder provided for each individual site and provided to the Sponsor or its designee at the start of the trial. Questions referring to a specific serious adverse event occurring in a study patient should be directed to the local Clinical Research contact person specified in the investigator folder provided for the site.

9.2.4 Reporting Serious Adverse Events to Regulatory Agencies and Review Boards

The need for an expedited report to regulatory authorities will be determined by the Sponsor's Medical Monitor. All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the applicable regulatory authority (FDA in the US and to Health Canada in Canada). The Sponsor will notify investigators of all such SAEs and these reports must be submitted by the investigators to the IRB/EC. In Europe, these SAEs will be submitted to the national competent authorities, EudraVigilance and to ECs according to national regulations.

9.3 Cardiac Toxicity Monitoring

As anthracyclines are known to have an adverse effect on cardiac function, each patient's cardiac function will be monitored through the Treatment and Follow-up Phases. Any left ventricular ejection fraction below 50% will be recorded as an adverse event. Any decrease in LVEF >10% resulting in a nadir LVEF <50% will be reported as an SAE. All randomized patients must have an ECHO or MUGA at:

- 1) Pre-Treatment
- 2) after the LAST induction that the patient receives
 - a. Responding patients after one or two inductions are assessed 30- 45 days after the start of the last induction or before the start of consolidation, whichever is later
 - b. Non-responding patients will be assessed prior to the start of salvage therapy or 30- 45 days after the start of the last induction if salvage treatment is not given.
- 3) Day 150 or 45 days from last treatment whichever is later
 - a. ALL patients must receive an ECHO or MUGA 150 days (\pm 10 days) from date of randomization. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 4) Follow-up Period
 - a. If the left ventricular ejection fraction is reduced >10% to below 50% from the baseline assessment at the last Treatment Phase measurement, left ventricular ejection fraction will continue to be monitored every 3 months until a return to baseline or 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

All cardiac assessments with ECHO/MUGA scans must be read locally for patient care. Assessments will also be sent to a central cardiac vendor who will digitize the scans for review at a later date. Details will be provided in the cardiac vendor's manual.

9.4 Laboratory Data

Laboratory data obtained according to the schedule of assessments will be recorded on the CRF or other data collection instrument. Only laboratory data requested by the protocol need be recorded unless specific findings result in a clinical event such as an adverse event or documentation of peripheral blood count recovery. These results will be collected.

9.4.1 Copper Assessment

Patients will have serum copper assessed routinely until levels return to baseline and the percentage of patients with persistent (>1 year) copper elevations will be reported. Also, patients with persistently elevated serum copper will be evaluated for clinical abnormalities associated with copper toxicity (e.g. unexplained increase in liver function

tests). Serum copper elevations are laboratory values and are not reported as adverse events unless associated clinical signs and symptoms of copper toxicity. All randomized patients must have a serum copper assessment at:

- 5) Pre-Treatment
- 6) after the LAST induction that the patient receives
 - a. Responding patients after one or two inductions are assessed 30- 45 days after the start of the last induction or before the start of consolidation, whichever is later
 - b. Non-responding patients will be assessed prior to the start of salvage therapy or 30- 45 days after the start of the last induction if salvage treatment is not given.
- 7) Day 150 or 45 days from last treatment whichever is later
 - a. ALL patients must have a serum copper assessment 150 days (± 10 days) from date of randomization. This is required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 8) Follow-up Period
 - a. If elevated copper (20% above ULN) persists at Day 150, perform monthly until abnormality returns to baseline or 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

Copper data will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection and processing and communication of results will be provided in a separate laboratory manual.

9.4.2 Molecular Mutations

Molecular mutation data for CEBPA, FLT3, and NPM1 will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection, and processing and communication of results will be provided in a separate laboratory manual.

9.4.3 Cytogenetic Assessments

Patients with apparent de novo disease may qualify for the study if they have myelodysplastic syndrome-related cytogenetic abnormalities (See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸ for a list of those abnormalities). Cytogenetic results must be available prior to randomization for these patients. If the institution does not perform cytogenetics or does not perform the test rapidly enough to initiate timely treatment, the sponsor has made a central laboratory available. For the sponsor to reimburse the testing, the patient must sign an abbreviated informed consent

form specific to this assessment and must meet some basic inclusion criteria (e.g. age of patient). Results will be rapidly (within 24 hours) reported to the institution and will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection, and processing and communication of results will be provided in a separate laboratory manual. If a patient has clear documentation of MDS AML, t -AML or $CMMoL$ AML (see Table 3: Documents Required for Registering a Patient), it is desirable, but not necessary to have the cytogenetics at randomization.

10.0 Other Evaluations

10.1 Pharmacokinetic Evaluations

Plasma concentration data collected from PK assessment from CPX-351 treated patients will be subjected to non-linear mixed-effect modeling (using the NONMEM program) analysis to obtain population PK parameter estimates. A population PK modeling approach will be used to describe plasma concentrations of cytarabine and daunorubicin following CPX-351 administration in the targeted patient population. Pharmacokinetic parameters such as clearance (CL) and volume (V) for cytarabine and daunorubicin will be defined for patients receiving CPX-351. In the analysis, a number of covariates, including demographic variables (e.g., age, gender, body weight, and race), clinical laboratory markers (e.g., AST, ALT, Creatinine Clearance), and concomitant medications will be evaluated to determine if they contribute to differences in the PK estimates among individuals. A separate PK analysis plan will be prepared prior to data analysis.

10.2 Medical Resource Use

Medical resource use (MRU) data will be collected for all study participants and analyzed by health outcomes (overall survival and response (CR+CRi) for CPX-351 vs. control arms. The MRU data collected in the trial will be used to identify costs associated with planned induction and consolidation treatment and for unplanned medical interventions necessary for patient support. Specific MRU data collected will include but may not be limited to:

- hospitalization nights (general ward and intensive care);
- blood product support (PRBC, Platelets, other);
- non-chemotherapy drugs (anti-infectives, growth factors, etc.); and
- AML chemotherapy (induction vs. consolidation).

11.0 Statistical Considerations

11.1 Study Overview

This is a randomized phase III study with equal allocation to each of the two treatments: 100 u/m^2 of CPX-351 (arm A) and standard of care (7+3, arm B). This study is designed to assess the efficacy and confirm the safety of 100 u/m^2 of CPX-351 compared to the standard of care (7+3). A total of 240 patients will be accrued and randomized to obtain 220 evaluable patients. This study will use a dynamic allocation procedure to allocate an equal number of patients to each of the treatment regimens. The procedure will balance

the marginal distribution of the stratification factors between these treatment regimens (see Section 4.1 for stratification factors).

11.2 Primary and Secondary Endpoints

11.2.1 Primary Endpoint

The primary objective of this study is to compare overall survival (OS), as defined in Section 8.2. All patients who have signed a consent form and have been randomized will be evaluable for overall survival.

11.2.2 Secondary Endpoints

Secondary efficacy endpoints include overall post induction response (CR+CRi) rate, best response (CR+CRi) rate (after completion of the treatment phase), remission duration (relapse-free survival) and event-free survival (EFS) as defined in Section 8.

Additional endpoints also include the rate of morphologic leukemia-free state, the rate of transfer for stem cell transplant and the following safety assessments: Deaths, SAEs, AEs, laboratory tests, vital signs, ECG, and echocardiography. In addition early (by Day 30 and 60) deaths will be monitored.

11.3 Sample Size and Power Justification for Primary Endpoint

The study will accrue 220 evaluable patients (110 per arm). An additional 20 patients (10 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on evaluable patients only and will be referred to as “patients” throughout the remainder of the statistical section. Assuming a uniform recruitment of 135 evaluable patients per year, 1.65 years will be required to complete enrollment of 220 patients. Furthermore, patients will be followed until the last patient enrolled has been followed for ≥ 1.2 years. Assuming exponential survival, and a median OS of 6 months in the control arm (Arm B), 190 deaths are expected to occur after opening of the study, resulting in a study with 94% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.6 between the two treatment arms. Total time for study completion is approximately 2.85 years.

A hazard ratio of 0.41 was observed in the 204 study for sAML patients. To approximate the hazard ratio to be expected in the Phase III study, we assumed one half the efficacy observed in Phase II which would require a sample size sufficient to detect a hazard ratio of approximately 0.60. This study is designed to have 94% rather than 90% power for the primary endpoint to assure that the sensitivity analysis which accounts for potential early drop-outs due to transplant is adequately powered to 90% for the same hazard ratio of 0.6 and the same patient population. Please see Section 11.5.5 for details on this sensitivity analysis.

11.4 Analysis of Primary Endpoint

Efficacy analysis will be performed on an intent to treat basis. A stratified log-rank test will be used to compare the experimental arm (Arm A) to the control arm (Arm B). The analysis for the primary endpoint will be performed after 190 deaths (86%) have occurred. Assuming exponential survival, uniform recruitment of 135 total eligible patients per year, an accrual period of 1.65 years, an additional follow-up period of 1.2 years and a median overall survival of 6 months, 190 events are expected to occur within 2.85 years after the opening of the study. The number of events is based on the alternative hypothesis. In addition, the distribution of OS in each arm will be estimated using the method of Kaplan-Meier by treatment group. The hazard ratio and OS rates at different time points, along with corresponding confidence intervals will be reported. Exploratory multivariate analyses will be performed to assess the treatment effect adjusting for key prognostic factors using the Cox proportional hazard regression model. This primary efficacy analysis will be performed on the *intent-to-treat population*.

A detailed statistical analysis plan specifying all planned analyses to be performed will be developed for this study before the analyses are conducted.

11.5 Analysis of Secondary Endpoints

Secondary efficacy endpoints include response (CR+CRi) rate, best response (CR+CRi) rate, remission duration (relapse-free survival), and event-free survival (EFS) as defined in Section 8.0.

In addition, we will perform a sensitivity analysis to account for patients transferred to HSCT (See Section 11.5.5).

All efficacy analyses will be performed on an intent-to-treat basis using the ITT analysis population.

11.5.1 Time dependent endpoints

Time dependent endpoints, such as remission duration and event-free survival (EFS), will be evaluated using a stratified log-rank test to compare the experimental arm to the control arm. In addition, the method of Kaplan-Meier will be used to estimate and display the distribution of these endpoints over time. Exploratory multivariate analyses will be performed to assess the treatment effect adjusting for key prognostic factors using the Cox proportional hazard regression model. Specific subgroup analyses will be performed to assess whether the treatment effect differs according to the stratification factors.

11.5.2 Binary Endpoints

The response (CR+CRi) rate and best response (CR+CRi) rate will be calculated based on the responses achieved as defined in section 8.4. The number of patients who achieve a CR or CRi will be divided by the number of patients in the intent-to-treat analysis population.

Likewise, the rate of achieving a morphologic leukemia-free state will be calculated as the number of patients who develop this state, as defined in section 8.6, divided by all randomized patients who have at least one evaluable post-randomization bone marrow assessment performed on Day 14-21 after the last induction.

The rate of stem cell transplant will be calculated by the number of patients starting conditioning treatment for stem cell transplant divided by the number of patients who have received at least one induction course.

The difference in response rate, morphologic leukemia-free rate and rate of transfer for stem cell transplant between the two treatment arms will be calculated using the Mantel-Haenszel test. These comparisons will be stratified by the stratification factors specified in Section 4.1. In addition, multivariate logistic regression analysis will be performed to assess the treatment effect while adjusting for key prognostic factors.

11.5.3 Analysis Populations

All efficacy analyses will be performed on an intent to treat basis using the *Intent-to-treat population* as defined in section 11.7. The analysis for transfer to stem cell transplant will be performed on the *per protocol population* as defined in section 11.7. Finally, the analysis on morphologic leukemia-free state will be performed on the *population* that achieves a morphologic leukemia-free state as defined in section 11.7.4. In addition a sensitivity analysis will be performed on all efficacy endpoints using the *per protocol population*. Further, the MDS subpopulation, consisting of those with MDS by history and patients with MDS by karyotype only; will be analyzed for OS, EFS, CR+CRi, best response, response duration and 60-day mortality.

11.5.4 Power Considerations for the Secondary Efficacy Endpoints

In the 204 study the observed hazard ratio for event-free survival of the 7+3 arm versus the CPX-351 arm was 1.79 (0.56) in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. This trial design with 220 patients total accrued over a period of 1.65 years with a 1.2 year follow-up yields 99% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 1.79 (0.56) between arms. The same trial design yields 94% power (with a one-sided alpha of 0.025) to detect a hazard ratio of 1.6. These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 56% in the CPX-351 arm and 32% in the 7+3 arm. This trial design with a total of 220 patients yields 94% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 24% in the CPX-351 arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 32%.

11.5.5 Sensitivity Analysis and Power considerations for Sensitivity Analysis

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time

of transplant. This analysis will account for early drop-out due to transplant and will be performed on the ITT population. To minimize bias due to transplant, stratification by risk which includes age (see Section 4.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 220 patients accrued in 1.65 years, followed for 1.2 years, median OS in control group 6 months. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60.¹⁷ We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60.

11.6 Safety Analysis

Safety data will be analyzed and reported for all patients in the *safety population* as defined in section 11.7. Safety data will be summarized and will include hematology, coagulation, chemistries, urinalysis, vital signs, ECG, echocardiography and adverse events (AEs). AEs will be coded using the MedDRA coding dictionary. Laboratory values will be summarized both by actual result and by toxicity grade. The maximum grade for each type of toxicity will be recorded and reported for each patient, and frequency tables will be reviewed to determine toxicity patterns.

The laboratory data, vital signs, ECG, and echocardiography will be summarized using descriptive statistics (n, mean, standard deviation, median, min and max) at each scheduled time point. The number and proportion of patients with reported AEs will be tabulated by treatment group.

Early death rates (by Day 30 and 60) will be evaluated separately for each arm by the number of deaths occurring in those time intervals divided by the total number of patients in the respective arm.

All patients will have serum copper levels assessed at baseline prior to the first dose, after the last induction and at Day 150. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels. The proportion of patients with elevated serum copper levels after the end of treatment with CPX-351 or 7+3 will be determined for each treatment arm. Comparisons

between arms will be made using the Mantel-Haenszel test. These comparisons will be stratified by the stratification factors specified in Section 4.1.

A Data and Safety Monitoring Board will oversee the conduct of the study. The Board consists of at least two hematologists, one cardiologist, and one statistician. The committee meets at specified intervals and reviews safety data including day 30 and 60 deaths and SAEs. This Board will be responsible for decisions regarding possible termination and/or early reporting of the study.

11.7 Analysis Populations

11.7.1 Intent-to-treat Population

The intent-to-treat population is all patients who have been randomized to the trial. Patients are assigned to treatment arms based on what they were “randomized” to receive. This is the primary efficacy population.

11.7.2 Safety Population:

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin) and have at least one post-baseline safety follow-up. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

11.7.3 Per Protocol Population:

These patients are a subset of the intent-to-treat population. The per-protocol population includes all patients who have met inclusion/exclusion criteria and have received at least one dose. The analysis of transfer to stem-cell transplant will be performed on this study population.

11.7.4 Morphologic Leukemia-free State Population

These patients are a subset of the per-protocol population. The morphologic leukemia-free state (MLS) population includes all randomized patients who have met inclusion/exclusion criteria, have received at least one dose and have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction.

11.7.5 Summary of Analysis Populations

Population	OS	EFS	CR/CRi rate*	CR/CRi duration*	MLS	30/60Day Mortality	SAE	Grade >3 AE	Labs
ITT	X	X	X	X					
Per-protocol	X	X	X	X					
MLS			X	X	X				
Safety						X	X	X	X

*includes best response

11.8 Timing of Analyses

An analysis of induction response (CR+CRi) and 60-day death rate will be performed approximately 90-120 days after the start of treatment of the last randomized patient, which is after all patients have been accrued, treated and recovered from induction treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized, treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR+CRi) and remission duration will be performed after the endpoint for the primary analysis has occurred.

12.0 Administrative, Regulatory and Ethical Issues

12.1 Direct Access to Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case report forms, all copies of test results, and study-related regulatory documents [e.g., Informed Consents, Institutional Review Board (IRB)/Ethics Committee (EC) approvals/correspondence, etc.] must be available at all times for regulatory agency inspection and review by the sponsor or its designee. During the periodic site monitoring visits, the source documents will be verified against data entered onto the CRF in order to assure that all data is accurately and completely reflected on the patient's CRF.

12.2 Study Monitoring and Quality Inspections/Audits

This study will be monitored by the sponsor or its designee according to GCP/ICH guidelines and EU legislation. A site visit will be held prior to initiation of patient enrollment. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail at the site visit. Subsequent to patient enrollment, a study site monitor from the sponsor or its designee will review the CRFs and source documents to ensure that the study is conducted according to the protocol and GCP/ICH guidelines and EU legislation. Sponsor's or its designee audit reports will be kept confidential.

To ensure compliance with GCP/ICH guidelines and EU legislation and all applicable regulatory requirements, the sponsor or its designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits or inspections can occur at any time during or after completion of the study. If audits or inspections occur, the Investigator and the Institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The investigator must promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

12.3 Ethics

This study will be conducted in accordance with local regulations, EU legislation, GCP, ICH guidelines and the Declaration of Helsinki. The Investigator at each site will be responsible for the overall conduct of the clinical trial for the site and will be responsible for ensuring the trial is conducted according to the protocol and all regulatory requirements and IRB/EC regulations.

12.4 Adherence to the Protocol

Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol will be conducted as described. If a change in the conduct is made to eliminate an immediate hazard, the Sponsor and the IRB/EC are notified immediately.

Deviations from the protocol will be considered in two categories, Protocol Violations and Protocol Deviations. Protocol Violations are those patients who are not eligible according to the inclusion/exclusion criteria in effect at the time of randomization. Protocol Deviations are all other non-compliance with the protocol, such as missing or skipped procedures or evaluations, evaluations performed outside given window, incorrect administration of investigational product, etc..

12.5 Protocol Revisions

12.5.1 North America

All revisions must be discussed with, and be prepared by, the Sponsor. If the revision is an Administrative Letter, the investigator should submit it to the IRB/EC for their information. If the revision is an Amendment, it will be signed by the Investigator. The investigator must submit the Amendment to the IRB/EC for review and approval prior to implementation. Documentation of approval signed by the Chairperson or designee of the IRB/EC must be sent to the Sponsor.

If an Amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB/EC for review and approval; (2) the revised form must be used to obtain consent from patients currently

enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

All revisions will be sent to the national competent authorities in North America.

12.5.2 Europe

If the revision is substantial (i.e. likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial or if they are otherwise significant) an amendment application must be submitted to the Ethics Committee and the national competent authorities.

12.6 Retention of Patient Records and Study Files

CRFs and other reports (e.g., investigator trial files, source documents, original, signed/dated informed consent forms) pertaining to this clinical investigation must be maintained for a minimum of 2 years following written notification by the sponsor of either regulatory approval or discontinuation of the development program. However, the investigator must obtain the Sponsor's agreement prior to disposal or transfer of responsibility for any study-related records.

12.7 Patient Confidentiality

The sponsor and/or its designee will preserve the confidentiality of all patients taking part in this trial. In the event of patient names inadvertently appearing on the trial documentation, this information will not be entered into the computer database for this trial. Representatives of the sponsor or its designee will seek access to clinical information only after approval to do so has been given by the patient and the relevant authorities. The data from this trial may be used in company publications and submissions to regulatory authorities.

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

What protected health information (PHI) will be collected from patients in this study
Who will have access to that information and why
Who will use or disclose that information

The rights of a research patient to revoke their authorization for use of their PHI:

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is/is not alive) at the end of their scheduled study period.

12.8 Informed Consent

Patients will be required to sign a statement of informed consent that meets the requirements of the US Code of Federal Regulations (21 CFR 50), Canadian regulations, European Community and European Union National Legislation, local regulations, ICH guidelines and the IRB/EC of the study center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the study and the date written consent was obtained.

Members of the treating team will review the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and alternative therapies including best supportive care. Patients must be informed that participation in the study is voluntary, he/she may withdraw from the study at any time and withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the study, as well as the efforts to maintain patient confidentiality will also be discussed.

This consent must be witnessed and dated and retained by the Investigator as part of the study records. A copy of the informed consent form must be given to the patient. In the event the patient is re-screened, the patient is not required to sign another informed consent form unless the patient is re-screened more than 30 days from the previous informed consent form signature date.

If an Experimental Subject's Bill of Rights is applicable in the Investigator's US state, that form must also be prepared and signed by each patient and retained as a part of the required study records. A copy of the Bill of Rights must be given to the patient or the patient's legally authorized representative.

A copy of the IRB approved consent form must be submitted to the Sponsor or its designee prior to shipment of drug supplies to the Investigator. Each patient's signed informed consent must be kept on file by the Investigator for regulatory authority and Sponsor (or its designee) inspection at any time.

For all US sites, the HIPAA Privacy Rule Authorization language must be included in the Informed Consent/authorization form (or a separate authorization document) and approved by the IRB (or Privacy Board). The elements of the HIPAA Privacy Rule Authorization are found in APPENDIX 6: Elements of the HIPAA Privacy Rule Authorization.

For all European Union sites the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data must be referred to http://www.cdt.org/privacy/eudirective/EU_Directive_.html#HD_NM_12).

The Declaration of Helsinki, as amended, recommendations (2008 version), guiding doctors in clinical research must be signed by the Investigator and returned to the Sponsor or its designee. A copy must also be kept on file by the Investigator.

The IRB/EC of an institution must approve the consent form document to be used at that center prior to its local activation; changes to the consent form during the course of the study will also require IRB/EC notification/approval.

The following elements must appear in the consent form: a description of the purpose of the study (indication, that the drug is investigational); potential side effects; potential benefits; study design; voluntary participation; and confidentiality. It is essential that the consent form contain a clear statement that gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the Sponsor and other agencies as necessary.

12.9 Publication Policy

The results of this study will be published. Authorship sequence for the final manuscript, interim publications and abstracts will be decided by the Sponsor in consultation with all investigators. This will generally be decided according to the number of patients accrued. Each contributing center (and participating investigator) will be acknowledged in the final manuscript. In addition, representatives for the Sponsor may be added, as appropriate, as co-authors.

To prevent premature disclosure of proprietary information and to protect the publication rights of other investigators in multicenter trials, the Sponsor requires review of written and oral presentation at least 45 days prior to initial submission to the publishing authority. If necessary to protect proprietary rights of information to be disclosed in the publication, the Sponsor may request a further 45 day delay in submission for publication, and the investigators agree to make all reasonable efforts to grant such further delay to the Sponsor.

If the investigators have not submitted the results for publication within six months after the completion of the final study report, the Sponsor will have the right to publish. In this case, the investigators will be given two months for review and comment prior to submission to the publisher.

No participant will present data from his/her study site separately from the rest of the study results, unless approved by the other investigators and by the Sponsor.

13.0 References

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14.0 APPENDIX 1: Patient Evaluation Flow Sheet – Treatment PhaseEach INDUCTION¹ and CONSOLIDATION:

Day:	Screening	1	2	3	4	5	6	7	10 ±1	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	Weekly ³ ±2	150 ⁸ ±10	End of Phase/Early Term.
Informed Consent ⁴	x																
Medical/Leukemia History	x																
Physical Exam	x									x				x			x
Vital Signs	x									x				x			x
ECOG Performance Status	x																x
ECG	x															x	x
Registration & Randomization	x																
Hematology	x	x		x		x		x	x	x	x	x	x	x	x		x
Biochemistry	x	x		x		x		x	x	x	x	x	x	x	x		x
Urinalysis	x																
Copper levels	x													x ⁹		x	
PK sampling ⁷		x		x		x											
Bone Marrow Evaluation	x									x ⁵	As needed to confirm response/persistence						
Chest X-ray/Chest CT	x																
Echocardiography/MUGA	x													x ⁹		x	
Response Assessment													x ⁶				
Cytogenetics/Molecular Studies	x	At the time of CR or CRi															
Adverse Events		Assess throughout Induction and Consolidation															x
Concomitant Medications		Assess throughout Induction and Consolidation															x
Treatment Administration	ARM A:	CPX-351	x		x		x ²										
	OR																
	ARM B:	Cytarabine	x	x	x	x	x	x ²	x ²								
		Daunorubicin	x	x	x ²												

¹The first induction may end prematurely if a second induction is necessary, see Section 4.6. The schedule of evaluations for the first induction is followed until the second induction starts, then the evaluations are followed as indicated in the flow sheet, beginning with Day 1

²Second inductions and consolidations of ARM A are CPX-351 on Days 1 and 3 and ARM B is 5 days of cytarabine and 2 days of daunorubicin, see Sections 4.6 & 4.7

³Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared

⁴Within 30 days prior to start of screening, if informed consent was collected, 30 days elapse and the patient is still not screened he/she must sign another ICF

⁵Required after each induction; (in case the Day 14 bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine effect and need for second induction); as needed thereafter to confirm response/persistence/relapse in second inductions & consolidations

⁶Induction(s) only; see Section 8.4.1 for details on when response is assessed.

⁷CPX-351 patients will be randomized to one of two PK sampling schedules: See Section 6.2 for the timing of pK draws

⁸Day 150 or 45 Days after the last treatment whichever is later

⁹After the last induction See Sections 9.3 & 9.4.1

15.0 APPENDIX 2: Patient Evaluation Flow Sheet –Follow-up

	Monthly for 1 Year (±10 Days)	Once Years 2-5	Early Termination
Patient status report	x	x	x
Hematology	x		x
Biochemistry	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from randomization, or the initiation of new therapy and/or relapse. (which ever is earliest)		
Copper levels	If elevated copper (>20% above ULN) persists at Day 150 perform monthly until abnormality returns to baseline or until 1 year from randomization.		
Bone Marrow Aspiration/Biopsy	For patients in CR or CRi <u>perform at any time that there is a suspicion of relapse</u> . For patients in CR, perform if peripheral blood counts fall below 1000/ μ L for ANC or 100,000/ μ L for platelets for >1 month or at any time there is suspicion of relapse. For patients in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a patient with a CRi recover to CR levels (\geq 1000/ μ L for ANC or \geq 100,000/ μ L for platelets), perform a bone marrow evaluation within 14 days to confirm CR. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following the initiation of new therapy and or relapse.		
Echocardiography or MUGA scan	If last LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline or until 1 year from randomization. Persistent reductions in LVEF of >10% and failing below 50% lasting >1 year are considered permanent sequelae.		
Adverse Events/Toxicity	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.		

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16.0 APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸

The eligible patient population based on WHO:

Therapy related AML:

Requires more than 20% blood or marrow blasts AND prior cytotoxic therapy for an unrelated disease:

- alkylating agents
- ionizing radiation therapy: large fields including active bone marrow
- topoisomerase II inhibitors
- others: antimetabolites, antitubulin agents

Acute myeloid leukemia with myelodysplasia-related changes:

Requires more than 20% blood or marrow blasts AND any of the following:

1. Previous history of myelodysplastic syndrome (MDS) requires:

Bone marrow evidence of dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryocytes	AND/OR	Unequivocal dysplasia in $< 10\%$ of cell in one or more myeloid cell lines with clonal abnormalities characteristic of MDS ¹
¹ Clonal abnormalities: Unbalanced changes: +8*, -7 or del(7q), -5 or del(5q); del(20q)*, -Y*, i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13) Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); inv(3)(q21q26.2), t(6;9)(p23;q34)		
*If the sole cytogenetic abnormality, also needs morphologic criteria with dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryocytes; all other clonal abnormalities are sufficient for a presumptive diagnosis		

OR

2. With myelodysplastic syndrome-related cytogenetic abnormalities:
 - Complex karyotype (defined as 3 or more chromosomal abnormalities).
 - Unbalanced: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
 - Balanced: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34)

AML with a history of CMMoL:

Requires more than 20% blood or marrow blasts AND a history of CMMoL which requires:

- Peripheral blood monocytes $> 1000/\mu\text{L}$
- Absence of Philadelphia chromosome or BCR-ABL1 fusion gene
- In the presence of eosinophilia, absence of rearrangements of PDGFRA or PDGFRB
- Presence of dysplasia in one or more myeloid lineages
- If myelodysplasia is absent/minimal the diagnosis of CMMoL may still be made if the above requirements are met and in addition there is the:
 - presence of acquired clonal cytogenetic or molecular genetic abnormality in hematopoietic cells OR
 - persistence of monocytes for ≥ 3 months and
 - all other causes of monocytes have been excluded
- At diagnosis of CMMoL there are fewer than 20% blasts (myeloblast, monoblast, promonocytes) in peripheral blood and bone marrow.

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17.0 APPENDIX 4: Performance Status – ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

18.0 APPENDIX 5: Common Terminology Criteria for Adverse Events V3.0 (CTCAE)

This 72 page document can be obtained as a pdf file from <http://ctep.cancer.gov>.
The publication date is December 12, 2003

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19.0 APPENDIX 6: Elements of the HIPAA Privacy Rule Authorization

- Written in plain language understandable to the patient or the representative;
- A “specific and meaningful” description of Protected Health Information (PHI) to be used and disclosed;
- The specific identification of the person/class authorized to make the use or disclosure;
- The specific identification of the persons/class to whom the covered entity may make the requested use or disclosure;
- Description of the purpose of the disclosure;
- An expiration date or event (i.e., “no expiration date” for data repository use, or “for the duration of a specific research study” permits use until end of study plus time for wrapping up and reporting);
- A statement of the patient’s right to revoke the authorization and any exceptions to the right to revoke;
- Conditions, if any, on authorization;
- A statement about possible re-disclosures of PHI by the recipient and that the PHI will no longer be protected by the Privacy Rule in the event of such re-disclosures; and
- The signature and date of the patient (or of the patient’s personal representative, along with the personal representative’s authority to act).

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20.0 APPENDIX 7: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR
MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Available at <http://www.wma.net/en/20activities/10ethics/10helsinki/>)

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21.0 APPENDIX 8: Anthracyclines Equivalents Guidelines

According to the exclusion criteria patients with a total lifetime anthracycline exposure exceeding the equivalent of 368 mg/m² of daunorubicin (or equivalent) prior to start of study therapy [100 u/m² of CPX-351 contains 44 mg/m² of daunorubicin x 3 doses (1 induction) = 132 mg/m² + 368 mg/m² = 500 mg/m² = maximum allowable limit of daunorubicin from all sources at the end of the 1st induction] are excluded from Protocol CLTR0310-301.

	Conversion factor*
Daunorubicin	1
Doxorubicin	2
Epirubicin	1
Idarubicin	4
Mitoxantrone	4.4

Multiply the number in the second column by the total cumulative dose a patient has received.

For example:

200mg/m² of mitoxantrone x 4.4(conversion factor) = 880mg/m²

This means 200mg/m² of mitoxantrone is equivalent to 880 mg/m² of daunorubicin

*Adapted from Keefe D., Anthracycline-Induced Cardiomyopathy. Seminars in Oncology, Vol 28, No 4, Suppl 12 (August), 2001: pp 2-7

Protocol CLTR0310-301

**PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS
CYTARABINE AND DAUNORUBICIN IN PATIENTS 60-75 YEARS OF AGE
WITH UNTREATED HIGH RISK (SECONDARY) AML.**

SPONSOR

Celator Pharmaceuticals, Inc.

Tel: [REDACTED]

Fax: [REDACTED]

MEDICAL MONITOR

Celator Pharmaceuticals, Inc.

Tel: [REDACTED]

Fax: [REDACTED]

Confidential

Version 2.3 4 November 2013

Replaces:

Version 2.2 9 October 2013

Version 2.1 17 September 2013 (never issued)

Version 2.0 12 March 2013

Version 1.0 May 22, 2012

Not for Publication

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

CPX351.C.PRTCL.00004.V2.3

Principal Investigator's Statement:

This protocol contains information that is confidential and proprietary to Celator Pharmaceuticals, the Sponsor. This information is provided to me for the purpose of conducting a clinical trial for the Sponsor. The contents of this protocol may be disclosed to study personnel under my supervision who need to know the contents for this purpose, as well as my Institutional Review Board(s) or Ethics Committee(s), subject to the following condition: the contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to the Sponsor of any such disclosure.

Any supplemental information that may be added to this document is also confidential and proprietary to the Sponsor and must be kept in confidence in the same manner as the contents of this protocol.

I further agree to conduct the clinical trial referred to above in accordance with all applicable government regulations, Good Clinical Practice, the Sponsor's guidelines and the procedures described in the protocol.

Investigator Signature

Date


Print Name

SIGNATURE PAGE FOR CELATOR PHARMACEUTICALS, INC.

Protocol: Protocol CLTR0310-301

Title: **PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS
CYTARABINE AND DAUNORUBICIN IN PATIENTS 60-75 YEARS OF
AGE WITH UNTREATED HIGH RISK (SECONDARY) AML**

Approved by the following:


Chief Medical Officer
Celator Pharmaceuticals, Inc.

Signature

Date

PROTOCOL SYNOPSIS

Title:

PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351
(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS CYTARABINE AND
DAUNORUBICIN IN PATIENTS 60-75 YEARS OF AGE WITH UNTREATED HIGH RISK
(SECONDARY) AML.

Sponsor:

Celator Pharmaceuticals, Inc.

Objectives:

Primary

- To confirm the efficacy of CPX-351 compared to "7+3" as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.

Secondary

- To confirm the safety of CPX-351
- To confirm the improvement in rate of morphologic leukemia free state¹, post-induction response (CR, CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR, CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare pharmacoeconomic differences between the treatment arms

Study Design:

This study is an open-label, parallel arm, randomized study where newly diagnosed AML including t-AML, AML in patients with a history of MDS or CMMoL, and de novo AML in patients with specific adverse karyotypic changes (per WHO definitions) are randomized to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). Patients are stratified by age and AML subtype at randomization to balance these prognostic factors across treatment arms:

Stratification Scheme:

Strata	
Age	Age 60-69 years OR Age 70-75
AML Type	<ul style="list-style-type: none"> Therapy-related AML: t-AML MDS transformed to AML with prior HMA treatment: MDSAML MDS transformed to AML without prior HMA treatment: MDSAML CMMoL transformed to AML: CMMoLAML De novo AML with MDS karyotype: de novoAML

Study enrollment duration is expected to be approximately 2 years. Efficacy and safety will be compared between the two study arms. Pharmacokinetic samples, at prespecified timepoints, will be collected in every CPX-351 patient.

Sample Size:

Three hundred (300) patients will be randomized with equal allocation between arms to obtain a minimum of 270 evaluable patients: 135 in the CPX-351 arm and 135 in the 7+3 arm.

Inclusion Criteria:

- Ability to understand and voluntarily give informed consent
- Age 60-75 years at the time of diagnosis of AML
- Pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the

peripheral blood or bone marrow)

- Confirmation of:
 - Therapy related AML: t-AML must have a documented history of prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease
 - AML with a history of myelodysplasia: MDS AML must have bone marrow documentation of prior MDS
 - AML with a history of CMMoL: CMMoL AML must have bone marrow documentation of prior CMMoL
 - De novo AML with karyotypic abnormalities characteristic of MDS: *de novo* AML must have cytogenetics with abnormalities per WHO.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Able to adhere to the study visit schedule and other protocol requirements
- Laboratory values fulfilling the following:
 - Serum creatinine < 2.0 mg/dL
 - Serum total bilirubin < 2.0 mg/dL, patients with Gilbert's Syndrome should contact the medical monitor
 - Serum alanine aminotransferase or aspartate aminotransferase < 3 times the ULN Note: If elevated liver enzymes, above the ULN, are related to disease; contact medical monitor to discuss.
- Cardiac ejection fraction $\geq 50\%$ by echocardiography or MUGA
- Patients with second malignancies in remission may be eligible if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic chemotherapy, documented by imaging, tumor marker studies, etc., at screening. Patients maintained on long-term non-chemotherapy treatment, e.g., hormonal therapy, are eligible.

Exclusion Criteria:

- Except for CMMoL, patients with history of myeloproliferative neoplasms (MPN) (defined as a history of essential thrombocythemia or polycythemia vera, or idiopathic myelofibrosis prior to the diagnosis of AML) or combined MDS/MPN are not eligible.
- Acute promyelocytic leukemia [t(15;17)] or favorable cytogenetics, including t(8;21) or inv16 if known at the time of randomization.
- Clinical evidence of active CNS leukemia
- Patients with active (uncontrolled, metastatic) second malignancies are excluded.
- Prior treatment intended for induction therapy of AML; only hydroxyurea is permitted for control of blood counts. For example, a patient with MDS that changes HMA dose and schedule after the diagnosis of AML is excluded. AML-type therapy, such as cytarabine alone ($>1\text{g}/\text{m}^2/\text{day}$) or cytarabine plus an anthracycline as well as prior HSCT are also excluded.
- Administration of any therapy for MDS (conventional or investigational) must be completed by 2 weeks prior to the first dose of study drug; in the event of rapidly proliferative disease use of hydroxyurea is permitted until 24 hours before the start of study treatment. Toxicities associated with prior MDS therapy must have recovered to grade 1 or less prior to start of treatment.
- Any major surgery or radiation therapy within four weeks.
- Patients with prior cumulative anthracycline exposure of greater than $368\text{ mg}/\text{m}^2$ daunorubicin (or equivalent).
- Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent
- Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)
- Active or uncontrolled infection. Patients with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥ 72 hrs.
- Current evidence of invasive fungal infection (blood or tissue culture); patients with recent fungal infection must have a subsequent negative cultures to be eligible; known HIV (new testing not

- required) or evidence of active hepatitis B or C infection (with rising transaminase values)
- Hypersensitivity to cytarabine, daunorubicin or liposomal products
- History of Wilson's disease or other copper-metabolism disorder

Study Drug:

CPX-351 (cytarabine:daunorubicin) Liposome Injection is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio shown to act synergistically in pre-clinical studies. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio.

CPX-351 is provided as a sterile, pyrogen-free, purple, lyophilized product in 50 mL glass, single-use vials. Each 50 mL vial after reconstitution contains 20 mL of CPX-351 (5 units/mL). Each unit (u) contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes suspended in sucrose. Product is stored at $5^{\circ} \pm 3^{\circ}\text{C}$.

Dosage Regimen:

1st Induction

Arm A (CPX-351): Study drug will be given intravenously at 100u/m^2 on days 1, 3 and 5 by approximately 90 minute infusion.

Arm B (7+3): Therapy will be administered intravenously with $100\text{mg/m}^2/\text{day}$ of cytarabine administered by continuous infusion for 7 days and 60mg/m^2 of daunorubicin given on days 1, 2 and 3.

2nd Induction

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving $>50\%$ reduction in % blasts count on the Day 14 bone marrow assessment, if safe to administer. In case the Day 14 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-10 days later, at the discretion of the treating physician, in order to determine effect and need for second induction. Patients who are not expected to receive second inductions include all patients with evidence of aplasia/hypoplasia ($<5\%$ blast count) and patients with equivocal bone marrow results who will have marrow exam repeated. Patients unable to achieve a response (CR+CRi) after two inductions are discontinued from the treatment period and followed for survival.

The second induction uses a modified dose and schedule:

Arm A (CPX-351): Study drug will be given intravenously at 100u/m^2 on days 1 and 3 by approximately 90 minute infusion.

Arm B (5+2): Therapy will be administered intravenously with $100\text{mg/m}^2/\text{day}$ of cytarabine administered by continuous infusion for 5 days and 60mg/m^2 of daunorubicin given on days 1 and 2.

Consolidation(s)

Only patients with documented response (CR or CRi) are eligible for chemotherapy consolidation. Prior to the first chemotherapy consolidation the LVEF must be documented to be $\geq 50\%$ and prior to every consolidation the PS must be 0-2. A second consolidation course may be given if the first consolidation was well tolerated. Consolidation with stem cell transplant (HSCT) is permitted either in place of chemotherapy consolidation or following chemotherapy consolidation. Consolidation therapy is highly recommended for every patient achieving CR or CRi. First consolidation must be given no earlier than 35 days after the start of the last induction and no later than 75 days after the start of the last induction. Patients must have recovered to $\text{ANC} > 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$ to be eligible for first or second consolidation. The second consolidation is administered 35-56 days after the start of the first consolidation.

Consolidation Dosing*

Arm A: CPX-351	
65 u/m^2	90 min infusion on Days 1 and 3
Arm B: 5+2	
Cytarabine 100mg/m^2	Continuous Infusion Days 1-5
Daunorubicin 60 mg/m^2	IV Days 1 and 2

*Alternative dosing is available for patients with $>500\text{mg/m}^2$ of anthracycline exposure, see Section 7.

Follow-up

Patients will be followed until death or up to 5 years following randomization. For Event-free Survival (EFS) evaluation, an event is documented as persistent AML after induction or relapse after achievement of CR/CRi or death. After documentation of persistent leukemia or relapse, follow-up for overall survival continues. At the start of HSCT or non-protocol consolidation treatment, AE data collection stops.

Efficacy Variables & Analysis:

- Primary endpoint:
 - Overall Survival (OS)
- Secondary endpoints:
 - Rate of morphologic leukemia-free state
 - Response rate (CR, CR+CRi), (morphologic, cytogenetic and molecular response)
 - Remission duration (relapse-free survival)
 - Event Free Survival

Safety Variables & Analysis:

Patients will be monitored for all clinical adverse events as well as laboratory evaluations.

- Induction Mortality: Day 30 and 60
- Serious Adverse Events
- Adverse Events: Grades 1-5 and Grades 3-5
- Laboratory Evaluations
 - Shift table analyses for hematology and chemistries
 - Time to hematologic recovery and proportion with prolonged cytopenias (≥ 56 days)
 - Copper levels: time to return to baseline levels
- Cardiac Evaluations
 - Cardiac AEs: Grades 1-5 and Grades 3-5
 - ECG changes (pre and post treatment)
 - LVEF changes (pre and post treatment)

Other Variables & Analysis:

PK Sampling for population PK: Patients randomized to CPX-351 are to have samples drawn for population PK. Five samples per patient are taken during the first induction course, all times are relative to the start of Day 1 infusion. CPX-351 patients will be sub-randomized to one of two PK sampling schedules: Schedule 1 Day 1: 45 min, 3 hrs, 8 hrs, Day 3 prior to dosing (48 hrs (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)) or Schedule 2: Day 1: End of Infusion, 2 hrs, 6 hrs, Day 5 prior to dosing (96 hr (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF.

Serum Copper Sampling: All patients, including those in the control arm, will have serum copper levels assessed at baseline prior to the first dose, on Day 5, Day 14, after the last induction dose and at Day 150. The data will be used to assess the variability of serum copper levels in the population as a whole and to determine the proportion of patients with persistently elevated serum copper levels after the end of treatment with CPX-351. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels.

Medical Resource Use: All patients will be assessed for causes and duration of hospitalization. Hospitalization duration associated with first induction, second induction, all inductions, first consolidation, and all consolidations will be assessed. The number of nights and percentage of nights spent in hospital on general wards vs. intensive care settings will be compared as well as duration of hospitalization associated with CR, CRi, and persistent AML. Cumulative hospitalization of Arm A vs. Arm B will be assessed. Similar assessments will be made for red blood cell transfusions, platelet transfusions and supportive care medications (e.g. antibiotics, anti-fungals, anti-virals and growth factors).

Independent Assessments:**Central Review of Diagnosis/Response:**

- Review of hematopathology reports documenting diagnosis of AML, prior AHD and/or chemotherapy exposure
- FISH or cytogenetics reports documenting karyotypic abnormalities characteristic of myelodysplasia.

- Review of hematopathology and peripheral blood reports documenting response.
- A charter will be reviewed and ratified prior to the initiation of the study

Data and Safety Monitoring Board:

- Consists of at least 2 hematologists+ 1 cardiologist + 1 statistician
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and end of study to review day 60 deaths and SAEs
- A single assessment of early deaths will be conducted after 75 patients (37 per arm) have been accrued and followed for 60 days.
- Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB using pre-defined early stopping rules.
- A charter will be reviewed and ratified prior to the initiation of the study

Cardiac Assessments:

- All assessments will be obtained and read locally for patient care. ECHO/MUGA scans will be sent to a central cardiac vendor who will archive the scans for review at a later date. Details will be provided in the cardiac vendor's manual.

Supportive care:

Infection Prophylaxis: is highly recommended during the period of profound neutropenia until ANC returns to 500 or greater. The choice of anti-infectives will be according to institutional protocol.

Growth Factor support: The use of growth factors will be according to institutional protocol.

Transfusion support: The use of transfusion support will be according to institutional protocol.

Statistical Analysis:

This is a randomized phase III study with equal allocation to each of the two treatments, CPX-351 (Arm A) and standard of care (7+3, Arm B). A total of 270 evaluable patients (135 patients per arm) will be enrolled in this study. Furthermore, we anticipate an accrual rate of 135 evaluable patients per year. An additional 30 patients (15 in each arm) will be accrued to account for ineligibilities and withdrawal of consent.

Primary Endpoint: The primary objective of this study is to compare overall survival (OS), as defined in section 8.2, in all randomized patients. A median OS of 0.526 years is anticipated in the control arm (Arm B). Assuming exponential survival, 135 patients per arm results in a study with 93.7% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 between the two treatment arms. The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 eligible patients per year, 2 years of accrual and 1.2 years of follow-up and a median overall survival of 0.526 years, 236 events are expected to occur within 3.2 years after the opening of the study.

Population PK: Plasma samples for population pharmacokinetic (PK) assessment will be analyzed for concentrations of cytarabine and daunorubicin and their associated metabolites following CPX-351 administration. A population PK modeling approach will be used to describe plasma concentrations for each analyte. In the analysis, a number of covariates, including age, weight, gender, and concomitant medications, will be evaluated to determine if they contribute to differences in the PK estimates among individuals. Details of the analysis will be described in a separate population PK analysis plan.

ABBREVIATIONS

7+3	Seven days of continuous infusion of cytarabine at 100 mg/m ² /day and three days of daunorubicin at 60 mg/m ² /day
5+2	Five days of continuous infusion of cytarabine at 100 mg/m ² /day and 2 days of daunorubicin at 60 mg/m ² /day
ADR	Adverse Drug Reaction
AE	Adverse Event
AHD	Antecedent Hematologic Disorders
ALL	Acute Lymphocytic Leukemia
ALT	Alanine Transaminase (SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Ara-U	Arabinosyluracil
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase (SGOT)
ATPase	Adenosine triphosphatase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
C _{max}	Maximum plasma concentration
CL	Clearance
CNS	Central nervous system
CPX-351	CPX-351 (cytarabine:daunorubicin) Liposome Injection
CR	Complete Remission
CRi	Complete Remission with incomplete hematologic recovery
CRF	Case Report Form
CMMoL	Chronic Myelomonocytic Leukemia
CTCAE	Common Terminology Criteria for Adverse Events
d	day
DEHP	di(2-ethylhexyl)phthalate
dL	deciliter
DSMB	Data and Safety Monitoring Board
DSPG	Distearoylphosphatidylglycerol
DSPC	Distearoylphosphatidylcholine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
ELN	European LeukemiaNet
EOI	End of Infusion
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
g	gram(s)
GCP	Good Clinical Practice

HCl	Hydrogen Chloride
HIPAA	Health Information Protection and Portability Act
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HOVON	Hemato-Oncologie voor Volwassenen Nederland
HP	High Purity
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ITT	Intent-to-treat
IRB/EC	Institutional Review Board/Ethics Committee
iv, IV	intravenous
K-M	Kaplan-Meier
L	liter
LDH	Lactate Dehydrogenase
LVEF	Left ventricular ejection fraction
m ²	square meters
MDR	Multi-drug Resistance
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
MLL	Mixed Lineage Leukemia
MPN	Myeloproliferative neoplasm
MLS	Morphologic Leukemia-free State
MRU	Medical Resource Usage
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
mw	molecular weight
N	Number, Population
NF	National Formulary
OS	Overall Survival
PD	Persistent Disease
PhEur	European Pharmacopoeia
PHI	Protected Health Information
PK	Pharmacokinetics
PS	Performance Status
q.s.	quantum sufficiat
RBC	Red blood cells
SAE	Serious Adverse Event
SD	Standard deviation
sAML	Secondary AML
T _{1/2}	Half-life
t-AML	Therapy-related AML
Tmax	Time of occurrence of Cmax
u	Units

μL	Microliter
ULN	Upper Limits of Normal
USP	United States Pharmacopeia
V	Volume
WHO	World Health Organization

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1 General Information

This document is a protocol for a human research study. This study is to be conducted according to United States and international standards of Good Clinical Practice (FDA Title 21 parts 11, 50, 54, 56, 312, International Conference on Harmonization and the Declaration of Helsinki), applicable government regulations and Institutional research policies and procedures.

2 Background Information

2.1 Acute Myeloid Leukemia in the Elderly and its Treatment

Acute myeloid leukemia represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate and excessive proliferation in the stem cell compartment result in accumulation of non-functional cells termed myeloblasts.²

Untreated AML in all ages is rapidly fatal, with patients dying on average within a few months of diagnosis. Even with treatment, particular groups of AML patients continue to have a poor prognosis. AML in the elderly (age ≥ 60) is associated with increased risk of not responding to therapy and increased risk of dying from the treatment. Appelbaum, et al.³ and Kantarjian, et al.⁴ summarize the factors that contribute to poor outcomes in elderly patients with AML. Risk factors that decrease patient tolerance to therapy or sensitivity of the leukemia to therapy include increasing age, poor performance status, co-morbid medical conditions, accumulated chromosomal abnormalities, adverse mutations, and multi-drug resistance.

There is broad overlap of these risk factors with most elderly AML patients having one or more adverse features. The poor results of treatment in elderly AML lead to a reluctance to treat elderly patients with intensive regimens designed to induce aplasia and complete remission.

Clearing the marrow of leukemia has historically been the only means of obtaining prolonged survival in AML patients. This is usually accomplished by use of intensive cytotoxic/cytoreductive therapy.⁵ The intensity of treatment needed to induce aplasia and complete remission is associated with early mortality rates of 10-20% in elderly patients considered fit for intensive therapy and is higher in patients with co-morbidities and poor performance status.^{3,4,6-8}

Burnett, et al.⁹ published a study of 1273 fit elderly AML patients given intensive therapy. This trial identified cytogenetics, presenting white blood count, age and secondary AML as the main predictors of outcome. Clinical outcomes did not improve with: intensification of induction therapy (daunorubicin 50 mg/m² versus 35 mg/m² and cytarabine 400 mg/m² versus 200 mg/m²), increasing the duration of consolidation from three to four courses, or use of an MDR modulator (PSC-833).

A randomized study reported in 2009 showed that a double induction regimen with 90 mg/m² daunorubicin with cytarabine first induction followed by a second induction with intermediate dose cytarabine (1 g/m²) could be safely administered with high rates of

complete remission in older patients. The second induction was given even to those who had already achieved CR after first induction, a practice that is not routinely used in the US and Canada. This publication from the HOVON group noted improvement in remission rate when compared to a cytarabine plus 45 mg/m² daunorubicin regimen but no improvement in disease-free survival or overall survival was observed.¹⁰ At the present time, the HOVON study has not been replicated in elderly patients by any other group.

Another study by Fernandez, et al., reported success for the same 90 mg/m² daunorubicin dose versus 45 mg/m² when used for first induction for younger patients.¹¹ If a patient required a second induction, the dose of daunorubicin was reduced to 45 mg/m² for all patients. Responding patients were taken to transplant. Neither this study nor the HOVON study used daunorubicin 90 mg/m² for second induction courses or in consolidation and neither study demonstrated that 90 mg/m² is more effective than 60 mg/m². Although of great interest, neither regimen is ready to be used as the control arm in a comparative study with CPX-351.

The 7+3 regimen using 60 mg/m² daunorubicin has been, and continues to be, widely used in the U.S., Canada and the European Union and is supported by a large body of medical literature. Variations on the 7+3 regimen using different anthracyclines, different doses, and different schedules of cytarabine and daunorubicin all lead to the conclusion that this regimen remains acceptable as standard of care for older patients able to tolerate intensive chemotherapy.

The control regimen for this pivotal study with CPX-351 is the 7+3 regimen using 100 mg/m²/d cytarabine by continuous infusion for 7 days and 60 mg/m² of daunorubicin on days 1, 2, and 3. Celator proposes daunorubicin as the control anthracycline because that allows a direct comparison of CPX-351 which also delivers daunorubicin. In addition, because both study arms receive cytarabine and daunorubicin this study will be a direct test of whether molar ratio controlled drug delivery can improve antitumor efficacy. Celator also proposes that post-remission chemotherapy be as symmetrical as possible in both arms of the study and plans to reduce the intensity of consolidation with CPX-351 (reduced from 3 to 2 doses and from 100 units/m² to 65 units/m²) to match that of control (7+3 reduced to 5+2). These adjustments in post remission therapy with CPX-351 are intended to result in similar levels of myelosuppression during consolidation therapy.

After complete remission is achieved, leukemic cells likely remain in numbers too small to be detected with current diagnostic techniques. If no further post remission or consolidation therapy is given, almost all patients will eventually relapse.¹² Therefore, post-remission therapy is necessary to eliminate non-detectable disease and prevent or delay relapse. The best consolidation regimen has never been well defined. Generally, the intensity of the standard 7+3 induction therapy is reduced to "5+2" for consolidation, which is a five day continuous infusion of the same dose of cytarabine given during induction and two instead of three days of the anthracycline. Retaining cytarabine and daunorubicin and CPX-351 for use in consolidation has the major advantage of keeping the active antileukemia therapies restricted to cytarabine and daunorubicin in both arms

allows a better test of the hypothesis that ratiometric dosing explains the difference in observed efficacy and safety.

For patients at high risk of relapse (e.g. those with high-risk cytogenetics, antecedent hematologic disorder, or therapy-related AML), allogeneic stem cell transplantation (HSCT) is usually recommended if the patient is able to tolerate a transplant and has a suitable donor. This form of post remission therapy must be permitted for all patients on this study because its use as post remission therapy is associated with prolonged relapse free survival. Because of potential imbalances in use of HSCT, a formal sensitivity analysis will be performed in addition to an intent to treat analysis. The sensitivity analysis is performed by re-analyzing the data after censoring patients at the start of HSCT, so that survival potentially attributable to HSCT can be removed, isolating the contribution of study treatment.

Secondary AML is a term that has been used to cover a heterogeneous group of poor prognosis AML arising in a setting of prior treatment with cytotoxic agents or large field radiation therapy and/or antecedent hematologic disorders (AHD). At the chromosomal level, specific karyotypic abnormalities have been identified and linked to myelodysplasia. As a consequence, the term secondary AML is somewhat ambiguous and for the purposes of this trial, has been supplemented with specific WHO-based definitions of particular patient groups that have usually been grouped under the umbrella of secondary AML. This study is open to some but not all patient subsets grouped within secondary AML. Specifically included are patients with treatment-related AML, those with documented pre-existing myelodysplasia and CMMoL, and patients with de novo AML with specific chromosomal abnormalities linked to myelodysplasia per WHO criteria. Excluded are patients with MPN (except for CMMoL), MDS/MPN, and patients with multilineage dysplasia (per WHO) in the absence of a history of MDS or specific MDS-related cytogenetic abnormalities. The grounds for these exclusions are based on differences in the prognosis of these patient subsets, with low probability of response and poor survival among MPN and MDS/MPN patients and higher probability of response and survival among patients with multilineage dysplasia only. After excluding these patient subsets, the remaining patients still have high risk disease but have relatively similar prognosis. Patients eligible for this study continue to have poorer response rate, shorter duration of remission, and shorter overall survival than good risk de novo AML patients.¹³ If patient entry in the Phase II study in newly diagnosed patients (Study 204) is a guide to probable future patient accrual, the proportion of patients with high risk characteristics as defined above is 68/126 (54%) and after exclusion of patients with MPN or MDS/MPN is 58/126 patients (46%), suggesting that this study may access nearly half of all patients with AML in the 60-75 year age range and the majority (~65%) of patients with high risk AML.

Identifying patients with de novo AML eligible on the basis of cytogenetics will require waiting for the results of cytogenetics testing or performing a panel of FISH-based assays. Celator will make available a reference laboratory to perform cytogenetic assays with results available within 6 days; whereas local laboratories may require more time. It is understood that rapid initiation of treatment is preferred and that delaying onset of

treatment for 2-3 days beyond the initial work-up will be uncomfortable for patients and physicians alike. A review of the recent literature reveals that in a series of 1317 patients gathered from Cleveland Clinic and MD Anderson Hospitals¹⁴ longer time from diagnosis to treatment was not a significant factor in worsening rate of CR($p=0.63$) or reducing OS ($p=0.30$) in older patients. The authors concluded that delaying treatment did not seem harmful in older patients and patients may benefit from waiting for additional testing to return, allowing enrollment into studies that account for cytogenetic findings.

2.2 CombiPlex® Technology

In vitro studies have shown that antitumor activity can be enhanced when cytotoxic drugs are used in combination. This has led, over the years, to the use of drug combinations in the clinic such that cytotoxic drug combinations are now standard in many forms of cancer treatment. New anticancer drugs are typically first introduced in patients as single agents. After a maximum tolerated dose is determined for one agent, a second agent is added and the dose of one or both agents is adjusted on the basis of toxicity. The development of these combination regimens then is determined empirically on the basis of tolerability. However, in vitro, where the ratio of drugs used in combination can be controlled, it has been demonstrated that drug combinations providing synergy at one ratio may be simply additive or even antagonistic at other ratios.¹⁵ When individual free drugs are administered, each agent is handled differently by the body, resulting in varying distribution of the individual drugs to tumor sites which can result in drug ratios that are suboptimal or ineffective. Celator's technology is based on the findings that in vitro synergistic activity of antineoplastic drugs depends on specific drug ratios and that the in vivo activity of a combination depends on maintaining the synergistic ratio. In this way, the development of a particular chemotherapeutic regimen can be based on the most efficacious ratio rather than empirically based on toxicity.

The development of CPX-351 (cytarabine:daunorubicin) Liposome Injection was based on 1) defining a synergistic ratio of the two active moieties, cytarabine and daunorubicin, using cell-based screening assays and 2) designing a liposomal drug carrier to maintain this ratio after intravenous administration. This ratio was not based on the empirically-derived, toxicity-guided regimens currently used for cytarabine and anthracyclines.

2.3 Physical, Chemical and Pharmaceutical Information

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. These liposomes have a nominal diameter of approximately 100nm and are suspended in sucrose. Sterilization is achieved by filtration through a 0.22 μ m filter.

CPX-351 is provided as a sterile, pyrogen-free lyophilized formulation in 50 mL glass, single-use vials. Each vial contains 100 units of CPX-351 where each unit contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes. The lyophilized cake is

reconstituted with sterile water for injection to obtain a homogeneous dispersion at 5 units/mL. The composition of the formulation after reconstitution is listed in Table 1 below.

Table 1: Quantitative Composition

Component	mw	Amount per Vial	Amount per unit
Cytarabine, USP/PhEur	243	100 mg	1.0 mg
Daunorubicin HCl USP/ PhEur (reported as the free base)	528	44 mg	0.44 mg
Distearoylphosphatidylcholine	790	454 mg	4.5 mg
Distearoylphosphatidylglycerol	801	132 mg	1.3 mg
Cholesterol, HP	387	32 mg	0.3 mg
Copper gluconate, USP	454	92 mg	0.9 mg
Triethanolamine, NF	149	7 mg	0.07 mg
Sucrose, NF	342	2054 mg	20.54 mg

2.4 Product Label

CPX-351 (cytarabine:daunorubicin) LIPOSOME FOR INJECTION		100 units/Vial
Each unit contains 1.0 mg ($\pm 10\%$) Cytarabine and 0.44 mg ($\pm 10\%$) Daunorubicin (base) in liposomes containing DSPC, DSPG and cholesterol. Also contains copper as copper gluconate, triethanolamine and sucrose.		
Store refrigerated at 5°C ($\pm 3^\circ\text{C}$) in an upright position.		
FRAGILE: Do not drop		
Caution: New Drug – Limited by Federal Law to Investigational Use		
Manufactured for		
Celator Pharmaceuticals, Inc., [REDACTED]		
Lot #	Expiration Date:	

2.5 Pre-clinical Pharmacology & Toxicology

The pre-clinical pharmacology and toxicology are summarized in the Investigator's Brochure for CPX-351.

2.6 Brief Summary of Prior Clinical Studies

Three clinical studies have been completed with CPX-351 and a detailed presentation is available in the Investigator's Brochure. A brief summary of these studies is presented below.

2.6.1 Phase I Study of CPX-351: CLTR0305-101

The primary goal for this study was to establish the MTD for CPX-351 and recommend a dose for further study in a Phase II setting. Pharmacokinetic assessments were made at every dose level and patients were monitored for signs of antileukemic activity.

The dosage regimen was designed to mimic the 7-day drug exposure provided by conventional 7+3 treatment using a single induction course administering doses on Days

1, 3, and 5, by 90 minute infusion. Patients with AML (multiply relapsed, refractory, or with first CR duration of 6 months or less), ALL, and high risk MDS were eligible.

Dose limiting toxicities were observed at the 10th dose level: 134 u/m^2 (134 mg/m^2 cytarabine + 59 mg/m^2 daunorubicin). One patient had significant reduction in post treatment LVEF and as a result the Phase II studies included a cap (500 mg/m^2) on cumulative anthracycline dose after one induction course of CPX-351 and patients with significant pre-existing cardiac disease were excluded. Other dose-limiting toxicities included hypertensive crisis and prolonged (>56 days) cytopenias.

The Phase I study of CPX-351 assessed the concentrations of cytarabine, daunorubicin, uracil arabinoside, and daunorubicinol at multiple dose levels and found that they exhibited mono-exponential, first order elimination with minimal early phase distribution.

The day 1 (single dose) and day 5 (multiple dose) C_{max} and $\text{AUC}_{(0-1)}$ were linear and the 5:1 molar ratio of cytarabine to daunorubicin was maintained for up to 24 hours after dosing at all dose levels on days 1 and 5.

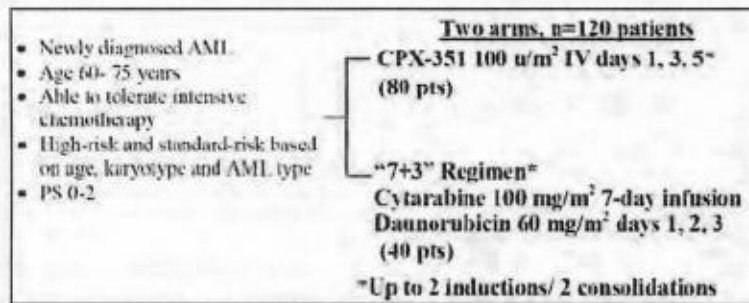
CPX-351 was found to have markedly prolonged mean half life for both cytarabine and daunorubicin, greater drug exposure (AUC), and higher peak plasma concentrations (C_{max}). Measurable drug levels were present seven days after the last infusion of CPX-351 (Study Day 12).

Response was observed in 1 of 3 multiply relapsed ALL and 10 of 43 AML patients. This was notable because most of the AML patients had already received cytarabine and daunorubicin in the past.

The maximally tolerated dose (101 u/m^2) was defined and persistence of the 5:1 molar ratio for up to 24 hours in the plasma was confirmed. Multiple responses in previously treated AML patients confirmed antileukemic activity.

2.6.2 Phase II Study of CPX-351: CLTR0308-204

The 204 study was designed as a randomized study comparing CPX-351 head-to-head against 7+3, in newly diagnosed, older (age 60-75) patients with AML. The comparison of encapsulated cytarabine and daunorubicin (CPX-351) versus free cytarabine and daunorubicin (7+3) would be fully interpretable for relative efficacy and safety. One hundred twenty-seven patients were randomized 2:1 to receive CPX-351 or 7+3. Response rate (CR+CRi) was the primary endpoint and superior response with a one-sided p-value of <0.1 was deemed sufficient for moving forward in development. Secondary endpoints were overall survival, event-free survival, CR+CRi duration, % leukemia-free after induction, safety and practicality of CPX-351 as consolidation therapy and the response rate of CPX-351 between de novo and secondary AML.



At entry patients were stratified by age (60-69 vs. 70-75), cytogenetics (< or ≥3 cytogenetic abnormalities), and type of AML (de novo vs. secondary). High risk patients were older (age 70 to <76) or had complex cytogenetics (≥3 cytogenetic abnormalities) or had secondary AML. Standard risk patients were younger (age 60-69), had non-complex cytogenetics (<3 abnormalities) and had de novo AML. After accrual was complete, [REDACTED] reviewed all of the cytogenetic reports and confirmed/corrected assignment of patients to <3 or ≥3 cytogenetic abnormalities and provided assessment of favorable, intermediate, and adverse cytogenetics per NCCN guidelines. Randomization and stratification were successful in balancing demographic and leukemia associated risk factors between the two study arms.

CPX-351 produced superior rates of leukemic-free state and response with similar duration of remission. It was notable that the improvement in response occurred predominately in the form of CRi (CR with incomplete hematologic recovery).

The study met the primary endpoint with a response rate of 66.7% compared to 51.2% with a p-value of 0.0712. Further analysis of response according to the stratification factors demonstrated consistent benefit for CPX-351 in response rate across every subgroup.

Kaplan-Meier (K-M) analysis after a minimum follow up of 1-year demonstrated non-significant improvements for CPX-351 for Event Free Survival (EFS) and Overall Survival (OS) in the overall population and the high risk strata.

Induction mortality was assessed at Day 30 and 60. A lower rate of early mortality was observed for CPX-351 treated patients at 60 days (4/85, 4.7% vs. 6/41, 14.6%, p=0.053). This result is the best evidence that CPX-351 treatment is acceptably safe and suggests that rapid clearance of leukemia may assist in reducing the early death rate.

CPX-351 treatment was associated with greater myelosuppression and more prolonged cytopenias, higher frequency of febrile neutropenia (63.5% vs. 51.2%), infections (e.g. bacteremia (42.4% vs. 22%)), and bleeding events (e.g. epistaxis (36.5% vs. 19.5%)). Otherwise, adverse events were qualitatively similar between both study arms. The lower mortality rate at 30 and 60 days indicates that CPX-351 was safe in spite of the consequences of greater myelosuppression.

Observations of reduced early mortality and a significant survival advantage (HR=0.41, p=0.02) among secondary AML patients suggest that clinical benefit is likely for this patient group in Phase III.

2.6.3 Phase II Study of CPX-351: CLTR0308-205

This study compared CPX-351 (100u/m²; Day 1, 3, 5) with salvage therapy in first relapse AML patients. This trial planned to accrue 120 patients with a 2:1 randomization to CPX-351 or investigator's choice of first salvage treatment. Responding patients were expected to receive allogeneic stem cell transplant for consolidation if donors were available. The European Prognostic Index was used to stratify patients. The primary endpoint was survival at one year, which was expected to be approximately 30% based on the literature. Secondary endpoints were CR+CRi rate, remission duration, event-free survival and 30/60/90 day mortality.

CPX-351 was able to increase the rate of leukemia-free state (77% vs. 60%), CR + CRi rate (49% vs. 41%), and had comparable 60-day mortality (15% vs. 16%), and better 90-day mortality (19% vs. 30%). After 1-year of follow up there were trends favoring CPX-351 for event free survival (HR=0.66, p=0.08) and overall survival (HR=0.75, p=0.19) among all patients and a subset analysis of the unfavorable risk group by European Prognostic Index showed a significant improvement in overall survival (HR=0.55, p=0.02). The proportion of CPX-351 patients alive at 1-year was 37% vs. 30% for control, and the proportion of unfavorable risk patients alive was 30% vs. 10%. These results in younger (age 18-65) patients with first relapse AML demonstrate potential efficacy among all patient subgroups with the largest improvement noted among higher risk patients and are entirely consistent with the results from newly diagnosed older patients in Study 204.

In summary, data from the Phase I and both randomized Phase II studies demonstrate consistent high level activity in AML marked by measurable increases in leukemia-free state and clinical response (CR + CRi) in most risk groups when compared to conventional therapy. The greatest relative difference occurred in the highest risk groups in both Phase II studies. The accumulated data suggest that CPX-351 may be a suitable replacement for the 7+3 regimen as first-line treatment and may be a useful alternative to current salvage regimens in the second-line setting. The proposed Phase III study is designed to confirm improved survival in newly diagnosed AML patients at high risk of poor outcome because of antecedent hematologic disorder (e.g. MDS and CMMoL), prior cytotoxic treatment (T-AML), and chromosomal abnormalities specifically linked to myelodysplasia (per WHO criteria) in patients with apparently de novo AML.

2.6.4 Copper Background

Copper is an essential element that is a component of a number of metalloenzymes acting as oxidases (e.g. diamine oxidase, monoamine oxidase, cytochrome c oxidase). The median absorption of copper from food (by an American adult) is 1.0 to 1.6 mg/day. The tolerable Upper Intake Level for adults is 10 mg/day. A CPX-351 dose of 100 u/m², would administer 36 mg of elemental copper to a patient with a BSA of 2.0 m². Animal

toxicology data suggest that elevated copper levels generally returned to baseline 1 to 2 weeks after the last dose. No toxicity was seen in animal studies attributable to copper. The data from the clinical studies are consistent with the preclinical findings. Since CPX-351 contains copper (0.18 mg copper per unit, in the form of copper gluconate), serum total copper levels were monitored in the Phase I clinical study.

Copper levels in patients receiving 3 doses of CPX-351 at 101 u/m² were elevated on day 7 (2 days after the last dose) but returned to normal levels in most patients by day 14. All patients had serum copper levels in the normal range by day 42 after induction. No acute toxicities attributable to copper exposure were observed.

The lack of toxicity observed in animal studies and in clinical studies to date is attributed to two factors: (1) most of the copper administered remains encapsulated within the liposome for most of the time it is in circulation limiting bioavailability and (2) the probability of copper-related toxicity is a function of C (the exposure to bioavailable copper) x T (the duration of exposure). If the exposure to elevated copper levels is limited to a few weeks, the risk of acute toxicity is probably low. Copper handling diseases generally require years of exposure to elevated copper levels before the onset of symptoms.

In this trial, serum copper levels will be monitored until return to baseline ($\pm 20\%$). Copper elimination after CPX-351 is likely via biliary excretion and elimination in the feces. It is expected that eligible patients with relatively normal liver function and unobstructed biliary systems should be able to eliminate the copper administered within a few weeks. Liver function tests will be performed regularly to assess hepatic dysfunction, a common manifestation of copper-related toxicity.

3 Study Objectives and Rationale

3.1 Primary Objectives

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 yrs) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.

3.2 Secondary Objectives

- To confirm the safety of CPX-351
- To confirm the improvement in rate of leukemia-free state, post-induction response (CR, CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR, CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare Pharmacoeconomic differences between CPX-351 and control

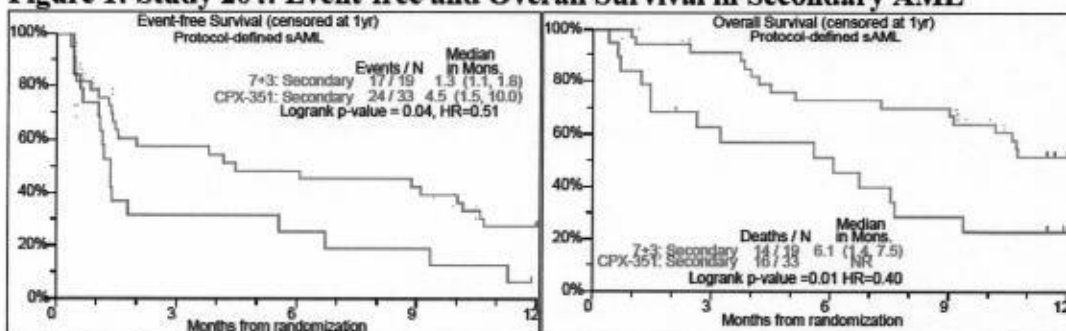
3.3 Study Rationale

The Phase I study demonstrated that an MTD in leukemia patients could be established for CPX-351 and that the intended 5:1 molar ratio of cytarabine to daunorubicin was maintained across multiple dose levels with markedly prolonged plasma half life of cytarabine and daunorubicin. At the MTD, CPX-351 was detectable in plasma at least 7 days after the last dose (Study Day 12). A substantial number of responses were observed in a population of patients with relapsed and refractory acute leukemia. This was notable because the majority had already received cytarabine and daunorubicin in the past. Data from this study was sufficient to give rise to two randomized Phase II trials, the first in newly diagnosed elderly AML patients (Study 204) and the second in first relapse patients age 18-65 (Study 205). Data from Study 204 provides the clinical rationale for this Phase III study.

Study 204 demonstrated consistent improvement in achievement of leukemia-free state and response (CR+CRi) across every AML subgroup studied. This included standard risk and high risk patients and within every constituent of the high risk group (age ≥ 70 , adverse cytogenetics, and secondary AML). Patient numbers were small in most subgroups, but the consistency of the response data is fairly persuasive that response differentials observed favoring CPX-351 are likely real.

As with response, CPX-351 appeared to improve event free survival across multiple subgroups although none were statistically significant. Analyses of the secondary AML subset indicated that this group of patients did particularly well relative to control by all efficacy and safety parameters. There were 52 patients with secondary AML by history, 33 randomized to CPX-351 and 19 randomized to 7+3. CPX-351 was superior for inducing a leukemia-free state (81.3% vs. 57.9%) and CR+CRi rate (57.6% vs. 31.6%), K-M analysis of event-free survival after 12 months minimum follow-up showed a significant difference in the CPX-351 arm (HR=0.51, p=0.04) and a significant difference in overall survival (HR=0.40, p=0.01).

Figure 1: Study 204: Event-free and Overall Survival in Secondary AML



When 30-day and 60-day mortality rates are assessed, CPX-351 is superior at 30-days (3.1% vs. 15.8%) and 60-days (6.1% vs. 31.6%) providing very strong evidence of acceptable safety in this higher risk subgroup.

The unexpected survival advantage in small numbers of secondary AML patients suggest a potential clinical benefit in this particular subgroup of patients that has traditionally had

poor outcome after conventional intensive treatment with median survival duration of approximately 6 months. The study hypothesis is that CPX-351 will improve overall survival in newly diagnosed patients with selected antecedent hematologic disorders transformed to AML and in de novo AML patients with specific chromosomal abnormalities linked with myelodysplasia when compared to conventional 7+3 treatment.

4 Study Design

This study is a randomized, open-label, parallel-arm, standard therapy-controlled Phase III trial in patients with selected antecedent hematologic disorders transformed to AML (t-AML, MDS-AML, and CMMoL-AML (with documented history of MDS or CMMoL prior to transformation) and de novo AML with karyotypic changes characteristic of myelodysplasia, per WHO). Study enrollment duration is expected to be approximately 2 years. On entry, patients are randomized to receive either CPX-351 or standard induction treatment with cytarabine and daunorubicin (7+3 regimen). Patients are stratified to balance the likelihood of response and survival between the two arms. The study is designed in 2 phases; the Treatment Phase where patients receive up to two induction and two consolidation courses and are intensively monitored for safety (early deaths, adverse events, metabolic changes, etc.) and secondary efficacy endpoints (CR+CRi rate, rate of HSCT) and a Follow-up Phase, which begins 30-days after the last induction or consolidation course and continues for up to 5 years from randomization where patients are monitored for the primary (survival) and additional efficacy outcomes (event-free survival, best response and response duration). In addition, pharmacokinetic samples, at prespecified timepoints, will be collected from every patient.

4.1 Stratification

Patients are stratified to balance these prognostic factors across treatment arms.

Table 2 Definition of Strata:

Factor	Strata
Age	60-69 vs. 70-75
AML type	Treatment-related AML MDS-AML with documented history of MDS <u>with</u> prior treatment with hypomethylating agents MDS-AML with documented history of MDS <u>without</u> prior treatment with hypomethylating agents <i>de novo</i> AML with karyotype characteristic of MDS CMMoL-AML with documented history of CMMoL

4.2 Patient Recruitment

All patients will be screened by a principal investigator or sub-investigator prior to entry on the study. An explanation of the study and discussion of the expected risks and benefits will be fully discussed with patients prior to the screening process in order for the patient to provide a voluntary written informed consent. Only eligible and consenting patients will be entered into the study.

At screening and prior to obtaining informed consent all prospective patients with newly diagnosed AML will have a detailed history of possible exposure to cytotoxic chemotherapy and radiation therapy. Documentation of prior cytotoxic therapy will be

obtained from discharge summaries, pharmacy records, radiation therapy treatment records, etc. Patients with a history of MDS or CMMoL that has transformed to AML will also have documentation (specifically bone marrow examination records) obtained confirming the diagnosis and its prior treatment. Patients with prior treatment are eligible but are substratified based on prior treatment with a hypomethylating agent for MDS. Finally, patients with apparent de novo AML may still be eligible if they have specific chromosomal abnormalities linked to MDS (e.g. complex cytogenetics, -7, -5, etc. See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸).

4.3 Registration/Randomization Procedures

After providing informed consent, eligible patients are registered by providing the following to the sponsor prior to randomization:

Table 3: Documents Required for Registering a Patient

Patient with a history of:	Required Documentation
MDS/CMMoL	<ul style="list-style-type: none"> Bone marrow biopsy/aspirate report, including peripheral blood smear, documenting MDS/CMMoL diagnosis in the past
Cytotoxic Chemotherapy	<ul style="list-style-type: none"> Medical records documenting prior chemotherapy and the condition being treated Chemotherapy administration records (preferred) Pharmacy records Other direct evidence of chemotherapy administration
Ionizing Radiotherapy	<ul style="list-style-type: none"> Medical records documenting prior radiation therapy, including the size of the radiation field, the total dose, and the condition being treated Other direct evidence of radiation therapy administration
Apparent de novo AML	<ul style="list-style-type: none"> FISH or cytogenetics assay documenting karyotypic abnormalities characteristic of myelodysplasia. Documentation of qualifying cytogenetic abnormality must be available prior to registering the patient.

Prior to randomization the sponsor must review the documentation and approve the patient to be randomized onto the study. The randomization is done via a telephonic or internet-based interactive randomization system. Specific details and procedures will be provided under separate cover. The system will request information on the patient's age, AML history, MDS/CMMoL history and chemotherapy/radiation history, as well as cytogenetics and will confirm eligibility. After randomization, investigators are provided, in writing, the patient number and treatment assignment. The patients pharmacokinetic schedule assignment will also be provided. The patient number is used on all documentation and correspondence.

The following information will be required for patient randomization:

- Treatment center and investigator information
- Patient's initials and date of birth
- Cytogenetics (specific karyotype if it is the sole basis of eligibility or unknown)
- Disease history: MDS/CMMoL documentation and/or chemotherapy/radiation documentation

4.4 Patient Sample Size

Three hundred (300) patients will be randomized to obtain approximately 270 evaluable patients. Equal numbers of patients will be randomized to CPX-351 (Arm A) or cytarabine and daunorubicin (Arm B, 7+3).

4.5 Induction

The initial induction course will begin within 24 hours of randomization. Following randomization, patients are monitored closely for response and safety. Depending on the type and extent of response as well as toxicity, the patient may continue on to consolidation therapy, receive a second induction, or be discontinued from the Treatment Phase and monitored in the Follow-up Phase.

Dosing for first induction:

- For **ARM A**: CPX-351 at 100u/m^2 will be administered on study days 1, 3 and 5
- For **ARM B**: 7+3: Cytarabine at a dose of $100\text{ mg/m}^2/\text{day}$ will be administered on study days 1-7 via continuous infusion and daunorubicin at a dose of $60\text{ mg/m}^2/\text{day}$ will be administered on days 1, 2 and 3.

4.6 Repeat of Induction

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving $>50\%$ reduction in % blasts count on the Day 14 bone marrow assessment, if safe to administer. In case the Day 14 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-10 days later, at the discretion of the treating physician, in order to determine effect and need for second induction. Patients who are not expected to receive second inductions include all patients with evidence of aplasia/hypoplasia ($<5\%$ blast count) and patients with equivocal bone marrow results who will have marrow exam repeated. Patients unable to achieve a response (CR+CRi) after two inductions are discontinued from the treatment period and followed for survival.

Dosing for second induction:

- For **ARM A**: CPX-351 at 100 u/m^2 will be administered on days 1 and 3
- For **ARM B**: Cytarabine at a dose of $100\text{ mg/m}^2/\text{day}$ will be administered on days 1-5 and daunorubicin at dose of 60 mg/m^2 will be administered on days 1 and 2 (5+2)
- The second induction must be started by Day 35.

4.7 Consolidation Therapy

Post-remission therapy in older patients with AML produces modest improvement in patient outcomes and should be extended to as many patients as possible. Only patients with documented response (CR or CRi) are eligible for consolidation. The bone marrow aspirate/biopsy report and peripheral blood count data is to be made available to the sponsor before beginning consolidation. Prior to the first consolidation the patient's

LVEF must be documented to be $\geq 50\%$ and prior to every consolidation the patients must have a PS of 0-2. First consolidation must be given no earlier than 35 days after the start of the last induction and no later than 75 days after the start of the last induction. Patients must have recovered to ANC $>500/\mu\text{L}$ and platelets $>50,000/\mu\text{L}$ to be eligible for first or second consolidation. The second consolidation is administered 35-56 days after the start of the first consolidation.

Dosing for consolidation:

- For **ARM A**: CPX-351 at 65 u/m^2 will be administered on days 1 and 3
- For **ARM B**: Cytarabine at a dose of $100 \text{ mg/m}^2/\text{day}$ will be administered on days 1-5 and daunorubicin at dose of 60 mg/m^2 will be administered on days 1 and 2 (5+2)

No other chemotherapy consolidation treatment is permitted. Only HSCT is permitted in place of, or following, chemotherapy consolidation.

A minority of patients will have prior anthracycline exposure and for these patients only, study treatment may push the cumulative exposure to anthracycline above 500 mg/m^2 (calculated as daunorubicin equivalents See APPENDIX 8: Anthracyclines Equivalents Guidelines). For patients who exceed 500 mg/m^2 , additional cardiac monitoring will be performed prior to all subsequent courses of anthracycline-containing therapy with ECHO/MUGA. Patients must be confirmed to have $>50\%$ LVEF without evidence of $\geq 10\%$ decrease in LVEF compared to baseline values. If there is any doubt about the cardiac safety of additional study therapy, investigators may contact the sponsor. In addition, investigators treating patients with cumulative anthracycline exposure $\geq 500 \text{ mg/m}^2$ will have the option to use an alternate consolidation regimen of intermediate dose cytarabine, 1.5 g/m^2 BID on Days 1, 3 and 5 (6 doses). Contact the sponsor prior to initiating this optional consolidation regimen.

Patients with less than 500 mg/m^2 cumulative anthracycline exposure, including study treatment, who have a $>10\%$ absolute decrease in LVEF to less than 50% , may receive the alternate consolidation regimen of intermediate dose cytarabine as described above.

4.8 Salvage Therapy

Patients who never achieve CR/CRi following induction and patients who achieve CR/CRi but later relapse may receive salvage therapy.

4.9 Follow-up Phase

The Follow-up Phase consists of routine visits or other patient contact to assess for the primary endpoint (survival) and other time to event endpoints (time to relapse). Patients begin the follow-up phase at different times depending on their treatment response. See Table 4:

Table 4: Follow-up Phase

CR	Begins after peripheral blood count recovery following the last course of treatment (Induction and/or Consolidations)
CRi	Begins after peripheral blood counts recover (to at least ANC to $\geq 500/\mu\text{L}$ and platelets to $\geq 50,000/\mu\text{L}$) or stabilize after the last course of treatment (Induction and/or Consolidations)

PD/treatment failure	Begins 30 days after documentation of persistent AML or discontinuation from study therapy if no benefit from further protocol-defined therapy is expected. The 30-day period is to document recovery from acute AEs
Adverse Event	Begins 30 days after an AE which, in the opinion of the investigator, requires discontinuation of any further protocol therapy. The 30 days allows for documentation of recovery from the AE.

The follow-up period continues until the death of the patient or up to 5 years from randomization. Patients who complete the Treatment Phase with significant residual non-hematopoietic toxicity will be followed for up to 4 additional weeks until toxicity resolves to \leq grade 1, stabilizes or initiation of new therapy, whichever occurs first. Patients with unresolved AEs after 4 weeks will have the events classified as permanent sequelae.

Follow-up for CR duration, EFS and Adverse Events (if applicable) are discontinued at the time of relapse, start of salvage or non-protocol treatment for leukemia (for persistent disease). All patients who have persistent or relapsed disease or who are transferred for stem cell transplant will be followed for up to 5 years for relapse and survival.

4.10 Study Modification/Discontinuation

Any modifications to the study will be documented in a revised protocol with a new assigned version. The revised protocol will have an appendix which will detail the revisions to the document.

The Sponsor may stop the trial early for the following reasons:

- Unacceptable toxicity
- Discontinuation of drug development
- Poor enrollment
- Request by a regulatory authority

In the case of study discontinuation, all participating institutions will be notified with procedures for discontinuing patients from the trial and informing the EC/IRBs (See Section 12.5).

4.11 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will periodically monitor the ongoing study for safety and efficacy considerations. The DSMB will consist of independent reviewers who are not directly involved in the conduct of the study and will advise the Sponsor of any trends or safety issues which may impact the study and/or the study patients. The DSMB will operate according to a charter which will be reviewed and ratified before the initiation of the study. The DSMB, at a minimum, will:

- Consist of at least 2 hematologists + 1 cardiologist + 1 statistician
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and at end of study to review day 60 deaths and SAEs
- Conduct a single interim analysis after 75 patients (37 per arm) have been evaluated for induction mortality with early stop rules. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB.

4.12 Central Review of Diagnosis and Response:

Participating centers are required to provide documentation of each patient's antecedent hematologic disorder or prior cytotoxic treatment before randomization (see Section 4.3). Every attempt will be made to confirm eligibility at time of randomization. After randomization, this documentation will be independently reviewed and the diagnosis confirmed. If there is doubt about the diagnosis of t-AML, MDS-AML or CMMoL-AML during the process of independent review, additional materials will be requested and reviewed. The specific requirements for diagnosis and details of the process for review and confirmation of diagnosis will be detailed in a separate operating plan.

In addition, an independent review of hematopathology and peripheral blood reports will be done to document response (CR+CRi) to therapy. A charter will be reviewed and ratified prior to the initiation of the study. The central reviewer will also be a non-voting member of the DSMB, providing the committee with progress reports on the quality of diagnostic and response documentation.

5 Selection and Withdrawal of Patients

5.1 Study Population

5.1.1 Inclusion criteria

- 5.1.1.1 Ability to understand and voluntarily sign an informed consent form
- 5.1.1.2 Age 60-75 years at the time of diagnosis of AML
- 5.1.1.3 Pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow)
- 5.1.1.4 Documentation of Antecedent Hematologic Disorder:
 - Therapy-related AML: Documentation of prior cytotoxic therapy or radiation therapy for an unrelated disease in a discharge summary or pharmacy records or radiation therapy records
 - MDS-AML: Bone marrow documentation of MDS prior to diagnosis of AML
 - CMMoL-AML: Bone marrow documentation of CMMoL prior to diagnosis of AML
 - *de novo*-AML with FISH or cytogenetic changes linked to MDS per WHO criteria (see APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸)
- 5.1.1.5 Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- 5.1.1.6 Able to adhere to the study visit schedule and other protocol requirements
- 5.1.1.7 Laboratory values fulfilling the following:
 - Serum creatinine < 2.0 mg/dL
 - Serum total bilirubin < 2.0 mg/dL, patients with Gilbert's Syndrome should contact the medical monitor

- Serum alanine aminotransferase or aspartate aminotransferase < 3 times the ULN. Note: If elevated liver enzymes are related to disease; contact medical monitor to discuss.

- 5.1.1.8 Cardiac ejection fraction $\geq 50\%$ by echocardiography or MUGA
- 5.1.1.9 Patients with second malignancies in remission may be eligible if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic chemotherapy, documented by imaging, tumor marker studies, etc., at screening. Patients maintained on long-term non-chemotherapy treatment, e.g., hormonal therapy, are eligible.

5.1.2 Exclusion Criteria

- 5.1.2.1 Except for CMMoL, patients with history of myeloproliferative neoplasms (MPN) (defined as a history of essential thrombocytosis or polycythemia vera, or idiopathic myelofibrosis prior to the diagnosis of AML) or combined MDS/MPN are not eligible.
- 5.1.2.2 Acute promyelocytic leukemia [t(15;17)] or favorable cytogenetics, including t(8;21) or inv 16 if known at the time of randomization.
- 5.1.2.3 Clinical evidence of active CNS leukemia
- 5.1.2.4 Patients with active (uncontrolled, metastatic) second malignancies are excluded.
- 5.1.2.5 Prior treatment intended for induction therapy of AML; only hydroxyurea is permitted for control of blood counts. For example, a patient with MDS that changes HMA dose and schedule after the diagnosis of AML is excluded. AML-type therapy, such as cytarabine alone ($>1\text{g}/\text{m}^2/\text{day}$) or cytarabine plus an anthracycline as well as prior HSCT are also excluded.
- 5.1.2.6 Administration of any therapy for MDS (conventional or investigational) must be completed by 2 weeks of the first dose of study drug; in the event of rapidly proliferative disease use of hydroxyurea is permitted until 24 hours before the start of study treatment. Toxicities associated with prior MDS therapy must have recovered to grade 1 or less prior to start of treatment.
- 5.1.2.7 Any major surgery or radiation therapy within four weeks
- 5.1.2.8 Patients with prior cumulative anthracycline exposure of greater than $368\text{ mg}/\text{m}^2$ daunorubicin (or equivalent), see APPENDIX 8: Anthracyclines Equivalents Guidelines
- 5.1.2.9 Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent
- 5.1.2.10 Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)

- 5.1.2.11 Active or uncontrolled infection; patients with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥ 72 hrs.
- 5.1.2.12 Current evidence of invasive fungal infection (blood or tissue culture); patients with recent fungal infection must have a subsequent negative cultures to be eligible; known HIV (new testing not required) or evidence of active hepatitis B or C infection (with rising transaminase values)
- 5.1.2.13 Hypersensitivity to cytarabine, daunorubicin or liposomal products
- 5.1.2.14 History of Wilson's disease or other copper-metabolism disorder

5.2 Withdrawal of Patients

Patients will be discontinued from the Treatment Phase and enter the Follow-up Phase for assessment of efficacy endpoints under the following circumstances:

- Completion of Treatment Phase
- Persistent disease: lack of a response to treatment
- Relapsed disease: re-appearance of disease following CR or CRi
- Unacceptable toxicity
- Patient non-compliance with protocol
- Administration of non-protocol chemotherapy
- Intercurrent illness which, in the judgment of the investigator, affects assessment of clinical status to a significant degree, and requires discontinuation of protocol therapy.

During any phase of the study, if a patient requests to stop treatment and/or follow-up, the patient will be discontinued and no further information will be collected. The patient will be classified as withdrawal of consent. Any patient that dies on or before Day 7 will be included in the intent-to-treat analysis but will also be replaced to ensure adequate study power.

6 Treatment of Patients

See APPENDIX 1: Patient Evaluation Flow Sheet

6.1 Pre-Treatment Evaluations

After providing informed consent, eligible patients are registered by providing documentation of high-risk (secondary) AML to the sponsor PRIOR to randomization. The list of required documents can be found in Section 4.3 on page 25.

The date of the first test or exam will be considered as the date of the screening visit.

Procedure	Evaluation	Timing
Informed Consent	It should be personally signed and dated by the patient. The responsible investigator must also personally sign and date the document. A copy of the Informed Consent must be given to the patient. The patient's study screening must be conspicuously noted in the source documentation.	Informed consent should be obtained prior to initiation of screening procedures. If the period between ICF signature date and screening visit is ≥ 30 days the patient must sign another ICF.

Procedure	Evaluation	Timing
Demography	Date of birth, sex, race, ethnicity	Within 14 days prior to randomization
Medical History	Complete medical history <ul style="list-style-type: none"> Resolved conditions Intermittent conditions Concurrent illnesses Previous surgeries 	Within 14 days prior to randomization
Leukemia History	<ul style="list-style-type: none"> Leukemia, MDS, CMMoL History Prior chemotherapies Prior hypomethylating agents 	Within 14 days prior to randomization
Physical Exam	Objective review of body systems Height Weight BSA ECOG Performance Status	Within 3 days prior to randomization
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Within 3 days prior to randomization
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Within 1 day prior to randomization
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Within 1 day prior to randomization
Copper levels	Serum copper (performed by a central laboratory)	Within 3 days prior to randomization
Urinalysis	pH specific gravity glucose protein ketones blood	Within 3 days prior to randomization
Bone Marrow Aspiration/Biopsy	Morphology	Within 14 days prior to randomization
Diagnostic Imaging	Chest X-ray or Chest CT Echocardiography or MUGA scan (sent to a central laboratory)	Within 28 days prior to randomization
ECG		Within 14 days prior to randomization

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Procedure	Evaluation	Timing
Cytogenetics	Cytogenetics (performed locally)	Within 3 months prior to randomization: patients may be randomized and treated prior to the cytogenetic test results; however, every attempt should be made to have the results prior to randomization
	Cytogenetics (performed by a central laboratory): For those centers that have a turn-around of 7 or more days, a central laboratory will be made available to screen de novo patients for eligible karyotypes (See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia ¹⁸ . A separate informed consent form is used to screen de novo patients for eligible karyotypes with a short eligibility checklist. See Section 9.4.3.	
Molecular Studies	Central or local laboratory evaluation of CEBPA, FLT3, and NPM1	Within 3 months prior to randomization: patients may be randomized and treated prior to receiving the results of molecular tests

6.2 Evaluation during Treatment Phase

Inductions and consolidations are administered as courses. A course consists of the administration of therapy with scheduled assessments to evaluate the response to treatment. The first induction may end before the completion of all evaluations if a second induction is necessary, (see Section 4.6). Induction is completed when a patient has

- A confirmed CR (see section 8.4)
- A CRi (see section 8.4) and is to begin consolidation treatment before hematologic count recovery
- Persistent/recurrent disease (PD/relapse)
- Response evaluation cannot be performed because of the patient's condition and no further study treatment can or will be administered.

Patients with a CR or CRi may receive up to two consolidation treatments. Evaluations on Days 1-7 must be performed on the day indicated; all other evaluations are to be performed on the Study Day indicated plus or minus 2 days. Each course requires the following evaluations:

Procedure	Evaluation	Timing
Physical Exam	Objective review of body systems Weight BSA	Days 14 and 42
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Days 14 and 42

Procedure	Evaluation	Timing
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Days 1, 3, 5, 7, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Days 1, 3, 5, 7, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase
PK sampling	Plasma concentrations for cytarabine and daunorubicin and metabolites (performed by bioanalytical laboratory)	CPX-351 patients will be sub-randomized to one of two PK sampling schedules during the first induction only, all times are relative to the start of Day 1 infusion: <u>Schedule 1:</u> Day 1: 45 min, 3 hrs, 8 hrs, Day 3 prior to dosing (48 hrs (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)) or <u>Schedule 2:</u> Day 1: End of Infusion, 2 hrs, 6 hrs, Day 5 prior to dosing (96 hr (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF. Four samples are collected from each patient randomized to CPX-351.
Copper levels	Serum Copper (performed by a central laboratory)	Induction 1: Day 5, (For Arm A: 10 minutes after completion of the infusion, Arm B any time on Day 5), Day 14; and after the last induction that the patient receives; See Section 9.4.1 for details
Bone Marrow Evaluation	Morphology	Required at Day 14-21 after every induction; Required at recovery to confirm response (CR/CRi) or persistent disease; in case Day 14-21 bone marrow is non-evaluable or assessment of a morphologic leukemia-free state is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine antileukemic effect and need for second induction.

Procedure	Evaluation	Timing
Cytogenetics Molecular Studies	Cytogenetics (performed locally) Molecular Studies (performed locally or by the central laboratory)	Required in patients with a CR or CRi with positive baseline findings (perform at the time of bone marrow assessment for CR or CRi). Optional in patients with normal baseline cytogenetics/molecular studies.
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	After the last induction that the patient receives and for patients with anthracycline exposure exceeding 500 mg/m ² prior to every course of daunorubicin-containing treatment; See Section 9.3 for details
Response Assessment		See Section 8.4.1
Adverse Events/Toxicity	CTCAE v.3 assessment	Continual assessment starting from the first dose until 30 days after completion of the Treatment Period.
Concomitant Medications	GCSF Anti-infectives	Continually assess during Treatment Period

6.3 Day 150 Evaluations

All patients randomized to this protocol must have the following assessments performed 150 (±10) days from randomization or 45 days after the last treatment, whichever is later. **These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or if they have been transferred for HSCT.**

	Evaluation	Timing
ECG		Day 150 ±10 days
Copper levels	Serum Copper (performed by a central laboratory)	Day 150 ±10 days See Section 9.4.1 for details
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	Day 150 ±10 days See Section 9.3 for details

6.4 Early Termination or End of Treatment Phase

Any patient that completes or discontinues treatment must have the following evaluations performed within 30 days after termination and prior to the initiation of any salvage therapy, if not performed within the last 30 days:

Procedure	Evaluation	Timing
Diagnostic Imaging	Echocardiography/MUGA	Within 30 days after discontinuation if a study has not been performed since last treatment or before the initiation of any non-protocol treatment
ECG		Within 30 days after discontinuation
Adverse Events/Toxicity	CTCAE v.3 assessment	Assess Adverse events that were ongoing at the time of discontinuation and record and report any new serious adverse events (up to 30 days after discontinuation)
Response Assessment	Best Response Reason for End of Treatment	

6.5 Evaluation during Follow-up Phase

The following evaluations are completed during the follow-up phase:

Procedure	Evaluation	Timing
Patient status report	Survival status	Once monthly until 1 year from randomization, after the first year record only the date of death or alive at Year 5 (Day 1825).
	Relapse status New anti-leukemic therapies	Once monthly until 1 year from randomization, after the first year record only the date of relapse and any new leukemic therapies.
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Once monthly until 1 year from randomization or the initiation of new therapy and/or relapse
Bone Marrow Evaluation	Morphology	For patients in CR or CRi <u>perform at any time that there is a suspicion of relapse.</u> For patients in CR, perform if peripheral blood counts fall below 1000/ μ L for ANC or 100,000/ μ L for platelets for >1 month or at any time there is suspicion of relapse. For patients in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a patient with a CRi recover to CR levels ($\geq 1000/\mu$ L for ANC or $\geq 100,000/\mu$ L for platelets), perform a bone marrow evaluation within 14 days to confirm CR. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following relapse.

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Procedure	Evaluation	Timing
Diagnostic Imaging	Echocardiography or MUGA	If last treatment phase or the day 150 LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline \pm 5% or until 1 year from randomization. Persistent reductions in LVEF of >10% with nadir values below 50% documented at 1 year are considered permanent sequelae.
Biochemistry	BUN Creatinine Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT Protein Calcium Albumin Glucose	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from randomization, or the initiation of new therapy and/or relapse. (whichever is earliest)
Copper levels	Serum Copper (performed by a central laboratory)	If elevated copper (>20% above ULN) persists at Day 150 perform monthly until abnormality returns to baseline or until 1 year from randomization.
Adverse Events/Toxicity	CTCAE v.3 assessment	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.

7 Drug Administration

The responsibility for treatment of patients rests with the individual investigator. Protocol treatment must begin within 24 hours of randomization.

First Induction:

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	100u/m ² /day	IV	90 minutes*	Days 1, 3 and 5
B	Cytarabine	100mg/m ² /day	IV	7 days	Days 1-7 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1, 2 and 3

Second Induction:

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	100u/m ² /day	IV	90 minutes*	Days 1 and 3
B	Cytarabine	100mg/m ² /day	IV	5 days	Days 1-5 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1 and 2

Consolidations (up to two are permitted):

Arm	Agent	Dose	Route	Duration	Schedule
A	CPX-351	65u/m ² /day	IV	90 minutes*	Days 1 and 3
B	Cytarabine	100mg/m ² /day	IV	5 days	Days 1-5 by continuous infusion
	Daunorubicin	60mg/m ² /day	IV Push	15 minutes	Days 1 and 2

*Approximately

Optional Consolidations only for patients with ≥ 500 mg/m² daunorubicin equivalent exposure:

Arm	Agent	Dose	Route	Duration	Schedule
A/B	Cytarabine	1.5 g/m ² /BID	IV	90 minutes	Days 1, 3 and 5

7.1 Drug Preparation and Administration**7.1.1 CPX-351****7.1.1.1 Drug Preparation**

The appropriate number of vials of CPX-351 (cytarabine:daunorubicin) Liposome Injection should be removed from the refrigerator prior to reconstitution. Reconstitute with 19 mL of sterile water for injection using a 20 mL syringe. Do not heat CPX-351 (cytarabine:daunorubicin) Liposome Injection. After reconstitution, invert vials gently 3-4 times and let rest for 15 minutes and repeat vial inversion prior to withdrawing drug for dilution. The concentration of the reconstituted dispersion is 5 u/mL. CPX-351 (cytarabine:daunorubicin) Liposome Injection should be diluted in approximately 500 mL of sodium chloride injection or dextrose injection.

The IV bags and infusion sets must be non-DEHP. Aseptic technique must be strictly observed throughout the handling of CPX-351 (cytarabine:daunorubicin) Liposome Injection since no bacteriostatic agent or preservative is present. The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection must be started within 4 hours of dilution. Vials are for single use. Unused material should be recorded as such and discarded according to institutional policies. Procedures for proper handling and disposal of anticancer drugs should be implemented.

7.1.1.2 Drug Administration

The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection will be performed through a central venous catheter, using an infusion pump to ensure that the drug is infused over the specified time period. Non-DEHP containing administration sets should be used. **Do not use an in-line filter.** CPX-351 should never be given by the intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes via an infusion pump. Flush the line to ensure administration of the full dose.

The dosage (total units and u/m²), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

7.1.2 Cytarabine and Daunorubicin "7+3"**7.1.2.1 Control Arm Drug Sourcing:**

In general, the drug products that may be used for the control arm will be sourced by the investigational site. Cytarabine and daunorubicin are approved in the US and Canada and

will be obtained from the appropriate market (US for investigational sites in the US, Canadian for sites in Canada). If for any reason, drug supplies for cytarabine or daunorubicin are unavailable or insufficient to complete all potential inductions and consolidations for a particular patient, contact the sponsor as soon as possible:

[REDACTED]

For as long as daunorubicin is listed on FDA's current drug shortage index and if daunorubicin cannot be obtained by the clinical site, Celator will provide daunorubicin. Celator will provide daunorubicin as Cerubidine[®], sourced from Canada and manufactured in Belgium, meeting USP specifications. Cerubidine will be provided on a per patient basis until US commercial supplies are available.

7.1.2.2 Cytarabine

Cytarabine is not provided as a study drug and must be supplied by the treating institution. Prepare and administer cytarabine according to institutional guidelines and the package insert. Below are general guidelines for preparation and administration.

The drug is available in vials of 100mg, 500mg, 1g and 2g – containing white lyophilized substance. The drug must be reconstituted prior to use.

A solution in which a slight haze develops should not be used, it should be discarded and another dose of the drug should be prepared. The ready solution should be stored at temperatures of 15-30°C. The solution should not be stored for prolonged periods of time and infusion should start as soon as feasible. All infusion solutions must be inspected visually for particulate matter and discoloration prior to administration. The dosage (total mg and mg/m²), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

Cytarabine is administered as a 7 day (for first induction) or 5 day (for second induction or consolidations) continuous intravenous infusion.

7.1.2.3 Daunorubicin

Daunorubicin is not provided as a study drug and must be supplied by the treating institution. Prepare and administer daunorubicin according to institutional guideline and the package insert. Below are general guidelines for preparation and administration.

The drug is provided as the HCl salt in vials containing a reddish lyophilized powder which should be reconstituted for infusion. Vials of 20 mg and 50 mg are available. The smaller packaging vials contain the equivalent of 20mg daunorubicin base (21.4 daunorubicin HCl - lyophilized powder) and 100mg mannitol. Each 50 mg vial contains 53.5 mg daunorubicin hydrochloride, equivalent to 50 mg daunorubicin base, and 250 mg of mannitol. The contents of the 20 mg vial should be reconstituted with 4 mL of Sterile Water for Injection, USP, and agitated gently until the material has completely dissolved. The sterile vial contents provide 20 mg of daunorubicin, with 5 mg of daunorubicin per

mL. The contents of the 50 mg vial should be reconstituted with 10 mL of Sterile Water for Injection, USP, and agitated gently until the material has completely dissolved. The sterile vial contents provide 50 mg of daunorubicin, with 5 mg of daunorubicin per mL. The reconstituted solution is stable for 24 hours at room temperature and 48 hours if refrigerated. The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP. Daunorubicin should not be administered mixed with other drugs or heparin. Store the unreconstituted powder according to label instructions at a controlled room temperature, 15-30°C (59-86°F). The dosage (total mg and mg/m²), start/stop time of the infusion, total volume infused, must all be documented in the patient's chart.

Daunorubicin Hydrochloride for Injection is administered intravenously into the tubing or sidearm in a rapidly flowing intravenous infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.

7.2 Drug Accountability

The study pharmacist or designee must maintain records of the delivery of CPX-351 to the study site, the inventory at the site, the use by each patient, and the disposition of unused product. These records should include dates, quantities, lot numbers, expiration dates and patient identifications. Institutions should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product received from the Sponsor. Records of storage conditions (temperature logs) must be kept for the entire period that CPX-351 is maintained at the institution.

7.3 Dose Reductions and Delays

It is the intention of the study to treat every patient at full dose. Doses may be delayed due to toxicities (for example hypersensitivity reactions). Any doses missed or delayed due to toxicity may be administered as soon as the patient has recovered from the toxicity. Investigators may contact the Medical Monitor to request delay or discontinuation of treatment if it is in the best interest of the patient. Toxicities will be graded using the CTCAE Version 3.0 (See APPENDIX 5: Common Terminology Criteria for Adverse Events V3.0 (CTCAE)). Toxicities for cytarabine and daunorubicin are relatively well known, and are outlined in the product information for each of these drugs.

7.4 Concomitant Therapy

7.4.1 Premedication

7.4.1.1 CPX-351

Nausea and vomiting:

Patients may be premedicated for nausea and vomiting according to institutional standards.

Hypersensitivity/Infusion-related reactions:

Patients will not be routinely premedicated for hypersensitivity or infusion-related reactions initially during the first infusion of the first treatment course. If the patient develops a hypersensitivity reaction then he/she should be pre-medicated at all subsequent infusions.

Suggested guidelines for management of hypersensitivity reactions:

Mild symptoms (e.g., mild flushing, rash, pruritus):

Stop infusion and supervise at bedside with monitoring of vital signs

Reinitiate infusion slowly (halving the rate of infusion) +/- premedication

Moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort):

Stop infusion and give IV diphenhydramine, 20-25 mg (or equivalent) and IV dexamethasone 10 mg.

Do not reinitiate infusion. Premedicate on re-treatment. Retreat at same dose and rate.

Severe/life-threatening symptoms (e.g. hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria):

Stop infusion. Administer IV diphenhydramine and dexamethasone as indicated above.

Add epinephrine (adrenaline) or bronchodilators if indicated. Do not reinitiate infusion.

Do not retreat. Report as a serious adverse event.

If hypersensitivity or infusion-related reactions become a clinically relevant toxicity, then premedication for hypersensitivity reactions will be instituted with drugs, doses and schedule according to each investigator's preference. Additionally, a decision may be made to prolong the infusion time to two hours or more.

7.4.1.2 Daunorubicin and Cytarabine

Premedication for daunorubicin and cytarabine are provided according to institutional policy and procedure.

7.4.2 Permitted therapy

Patients may receive ongoing supportive and palliative care (e.g. pain control) as clinically indicated throughout the study.

Infection Prophylaxis: Prophylactic use of anti-infectives is highly recommended during the period of profound neutropenia until ANC returns to 500/ μ L or greater. The choice of anti-infectives will be according to institutional protocol. Use of anti-infective agents as prophylaxis and treatment must be documented on the case report forms.

Growth Factor support: The use of growth factors will be according to institutional protocol and according to ASCO criteria.¹⁶ Use of growth factors must be documented on the case report forms.

Transfusion support: The use of transfusion support (RBCs and platelets) will be according to institutional protocol. Use of transfusion support must be documented on the case report forms.

7.4.3 Therapy that is not permitted

Other anti-cancer treatment and other investigational therapy(ies) are not permitted during the Treatment Phase. In the event of persistent disease or relapse the patient may receive other anti-leukemic therapies and is followed for survival.

7.5 Duration of Protocol Treatment

Patients may continue on study provided they have not met the criteria for discontinuation of therapy (See Section 5.2). The table below summarizes the expected duration of the Treatment Phase. Patients may receive up to two induction courses followed by up to two consolidation courses. After the Treatment Phase, patients are followed for up to 5 years from the time of randomization.

No. of Courses (Inductions or Consolidations)	Duration of Treatment Phase	Duration of Entire study
1	~ 42-56 days	5 years
2	~ 84-112 days	5 years
3	~ 126-168 days	5 years
4	~ 168-224 days	5 years

8 Assessment of Efficacy

8.1 Evaluable for Efficacy

All analyses will be based on the intent-to-treat principle; all randomized patients are evaluable for efficacy. Patients that die on or before Day 7 will be replaced.

8.2 Overall Survival

All randomized patients are assessed for overall survival. Overall survival is measured from the date of randomization to death from any cause, patients not known to have died at last follow-up are censored on the date they were last known to be alive. Patients will be followed for up to 5 years. Overall survival will be analyzed on an intent-to-treat basis with all randomized patients analyzed. A sensitivity analysis will be performed in which patient receiving hematopoietic bone marrow transplant are censored for survival at the start of conditioning therapy, to eliminate transplant as a confounding factor in the analysis of overall survival. For more detail, see Section 11.5.5.

8.3 Event-free Survival

All randomized patients are assessed for Event-free survival. Event-free survival is defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi or death from any cause, whichever comes first. Patients alive and not known to have any of these events are censored on the date they were last examined.

8.4 Response Assessment Criteria

During the Treatment Phase patients will be assessed for response according to the following criteria¹:

Complete remission (CR) ^a	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq 1.0 \times 10^9/L$ (1000/ μL); platelet count $\geq 100 \times 10^9/L$ (100,000/ μL); independence from red cell transfusions
CR with incomplete recovery (CRi) ^b	All CR criteria except for residual neutropenia ($< 1.0 \times 10^9/L$ [1000/ μL]) <u>or</u> thrombocytopenia ($< 100 \times 10^9/L$ [100,000/ μL])
Best Response	See Section 8.4.2
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia (blasts in peripheral blood, extramedullary leukemia, or persistence in the bone marrow)
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available at recovery
Relapse ^c	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

^aBone marrow assessment REQUIRED to confirm CR. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

^bBone marrow assessment REQUIRED to confirm CRi. Some patients may not achieve complete hematologic recovery prior to initiation of consolidation. CRi cannot be declared earlier than Day 35 to allow adequate time for documentation of peripheral blood recovery. Consolidation may begin no earlier than 35 days after the last induction course.

^cIn cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

The response of patients with no post-baseline bone marrow assessment is entered as not done.

8.4.1 Timing of response assessment

In general, the patient's response to induction therapy is made on the first day when all criteria for CR or treatment failure are met. The bone marrow assessment and the peripheral counts are not required to be performed on the same day but recovery of counts (including absence of peripheral blasts) must be performed within 14 days of the bone marrow assessment. The timing of other outcomes is recorded as follows:

1. After one or two induction course(s), PD is declared on the day of the bone marrow showing persistent AML.
2. CRi is declared on or after Day 35 following the last induction course when the patient's bone marrow (performed between day 35-56) demonstrates absence of leukemia and the peripheral blood counts have partially recovered but appear stable (performed at least twice between day 35-56).
3. For patients with sufficient blood count recovery ($ANC \geq 500/\mu L$ and platelets $\geq 50,000/\mu L$) that consolidation therapy is planned, CRi is declared on the day consolidation therapy is initiated but the peripheral counts have not met the full CR criteria. Consolidation must begin after day 35.

8.4.2 Best Response

Patients who complete the induction(s) with a response of CRi may be upgraded to a CR during or after consolidation if the patient's peripheral blood counts meet the criteria for CR after declaration of a CRi. To upgrade a response to CR both peripheral blood and bone marrow assessment are not required on the same day but must be obtained within a 14 day period of each other and all criteria for CR must be met (within a 14 day period must have full recovery AND be leukemia-free).

8.5 Remission Duration

Only patients achieving CR or CRi are assessed for remission duration. Remission duration is measured from the date of achievement of a remission (CR/CRi) until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined. For patients whose best response is upgraded from CRi to CR, remission duration for CR+CRi analyses will be calculated from date of CRi to date of relapse or death.

8.6 Morphologic Leukemia-free State

All randomized patients that have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction are assessed for morphologic leukemia-free state. Morphologic leukemia-free state is defined as bone marrow blasts $<5\%$ AND absence of Auer rods and/or extramedullary disease.¹

8.7 Stem Cell Transplant

The number and percentage of patients transferred for stem cell transplant will be quantitated and compared.

9 Assessment of Safety

9.1 Evaluable for Safety

All patients who have received at least one dose will be considered evaluable for safety.

9.2 Adverse Events

9.2.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An adverse event is considered serious if it meets any of the serious criteria listed in Section 9.2.2. To ensure no confusion or misunderstanding of the difference between the terms “serious” and “severe”, which are not synonymous, the following clarification is provided:

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Adverse events are to be recorded in the case report form from the start of the infusion on Day 1 to the last day of the treatment period, with the exception of serious adverse events. (See Section 9.2.2)

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An unexpected ADR is any adverse reaction not identified in nature or intensity in the current Investigator’s Brochure.

9.2.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any adverse event that at any dose:

Results in death (grade 5)
Is life-threatening
Requires inpatient hospitalization or prolongation of existing hospitalization
Results in persistent or significant disability or incapacity
Is a congenital anomaly/birth defect

These events are to be reported as serious from the start of the infusion on Day 1 to 30 days after completion of the treatment period. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate 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 or may require intervention to prevent one of the events listed above.

9.2.3 Serious Adverse Event Reporting Instructions

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax within 24 hours to the Sponsor or its designee. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information is sent to the Sponsor or its designee via the original Serious Adverse Event Form, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

The telephone and fax numbers of the local Clinical Research contact person and the contact person in the local department of Clinical Safety, specific to the site, must be listed in the investigator folder provided for each individual site and provided to the Sponsor or its designee at the start of the trial. Questions referring to a specific serious adverse event occurring in a study patient should be directed to the local Clinical Research contact person specified in the investigator folder provided for the site.

9.2.4 Reporting Serious Adverse Events to Regulatory Agencies and Review Boards

The need for an expedited report to regulatory authorities will be determined by the Sponsor's Medical Monitor. All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the applicable regulatory authority (FDA in the US and to Health Canada in Canada). The Sponsor will notify investigators of all such SAEs and these reports must be submitted by the investigators to the IRB/EC.

9.3 Cardiac Toxicity Monitoring

As anthracyclines are known to have an adverse effect on cardiac function, each patient's cardiac function will be monitored through the Treatment and Follow-up Phases. Any left ventricular ejection fraction below 50% will be recorded as an adverse event. Any decrease in LVEF >10% resulting in a nadir LVEF <50% will be reported as an SAE. All randomized patients must have LVEF assessed by ECHO or MUGA at:

- 1) Pre-Treatment
- 2) after the LAST induction that the patient receives:
 - a. Responding patients after one or two inductions are assessed 30- 45 days after the start of the last induction or before the start of consolidation, whichever is later

- b. Non-responding patients will be assessed prior to the start of salvage therapy or 30- 45 days after the start of the last induction if salvage treatment is not given.
- 3) Prior to every course of daunorubicin-containing treatment after patient exceeds 500 mg/m² daunorubicin equivalent exposure (including study treatment).
- 4) Day 150 or 45 days from last treatment whichever is later; ALL patients must receive an ECHO or MUGA 150 days (± 10 days) from date of randomization. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 5) Follow-up Period: If the left ventricular ejection fraction is reduced $>10\%$ to below 50% from the baseline assessment at the last Treatment Phase measurement, left ventricular ejection fraction will continue to be monitored every 3 months until a return to baseline ($\pm 5\%$) or 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

All cardiac assessments with ECHO/MUGA scans must be read locally for patient care. Assessments will also be sent to a central cardiac vendor who will digitize the scans for review at a later date. Details will be provided in the cardiac vendor's manual.

9.4 Laboratory Data

Laboratory data obtained according to the schedule of assessments will be recorded on the CRF or other data collection instrument. Only laboratory data requested by the protocol need be recorded unless specific findings result in a clinical event such as an adverse event or documentation of peripheral blood count recovery. These results will be collected.

9.4.1 Copper Assessment

Patients will have serum copper assessed routinely until levels return to baseline and the percentage of patients with persistent (>1 year) copper elevations will be reported. Also, patients with persistently elevated serum copper will be evaluated for clinical abnormalities associated with copper toxicity (e.g. unexplained increase in liver function tests). Serum copper elevations are laboratory values and are not reported as adverse events unless associated clinical signs and symptoms of copper toxicity. All randomized patients must have a serum copper assessment at:

- 1) Pre-Treatment
- 2) Induction 1: Day 5 (10 minutes after completion of infusion for Arm A patients; any time on Day 5 for Arm B patients)
- 3) Induction 1: Day 14
- 4) after the LAST induction that the patient receives
 - a. Responding patients after one or two inductions are assessed 30- 45 days after the start of the last induction or before the start of consolidation, whichever is later

- b. Non-responding patients will be assessed prior to the start of salvage therapy or 30- 45 days after the start of the last induction if salvage treatment is not given.
- 5) Day 150 or 45 days from last treatment whichever is later
 - a. ALL patients must have a serum copper assessment 150 days (± 10 days) from date of randomization. This is required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 6) Follow-up Period
 - a. If elevated copper (20% above ULN) persists at Day 150, perform monthly until abnormality returns to baseline or until 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

Copper data will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection and processing and communication of results will be provided in a separate laboratory manual. At the end of the study the percentage of patients with persistently elevated serum copper levels and the duration of elevated copper levels will be analyzed.

9.4.2 Molecular Mutations

Molecular mutation data for CEBPA, FLT3, and NPM1 will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection, and processing and communication of results will be provided in a separate laboratory manual.

9.4.3 Cytogenetic Assessments

Patients with apparent de novo disease may qualify for the study if they have myelodysplastic syndrome-related cytogenetic abnormalities (See APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸ for a list of those abnormalities). Cytogenetic results must be available prior to randomization for these patients. If the institution does not perform cytogenetics or does not perform the test rapidly enough to initiate timely treatment, the sponsor has made a central laboratory available. For the sponsor to reimburse the testing, the patient must sign an abbreviated informed consent form specific to this assessment and must meet some basic inclusion criteria (e.g. age of patient). Results will be rapidly (within 24 hours) reported to the institution and will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection, and processing and communication of results will be provided in a separate laboratory manual. If a patient has clear documentation of MDS/AML, t-AML or CMML/AML (see Table 3: Documents Required for Registering a Patient), it is desirable, but not necessary to have the cytogenetics at randomization.

10 Other Evaluations

10.1 Pharmacokinetic Evaluations

Plasma concentration data collected from PK assessment from CPX-351 treated patients will be subjected to non-linear mixed-effect modeling (using the NONMEM program) analysis to obtain population PK parameter estimates. A population PK modeling approach will be used to describe plasma concentrations of cytarabine and daunorubicin following CPX-351 administration in the targeted patient population. Pharmacokinetic parameters such as clearance (CL) and volume (V) for cytarabine and daunorubicin will be defined for patients receiving CPX-351. In the analysis, a number of covariates, including demographic variables (e.g., age, gender, body weight, and race), clinical laboratory markers (e.g., AST, ALT, Creatinine Clearance), and concomitant medications will be evaluated to determine if they contribute to differences in the PK estimates among individuals. A separate PK analysis plan will be prepared prior to data analysis.

Patients randomized to CPX-351 are to have samples drawn for population PK. Five samples per patient are taken during the first induction course. All times are relative to the start of Day 1 infusion. CPX-351 patients will be sub-randomized to one of two PK sampling schedules:

- Schedule 1: Day 1: 45 min, 3 hours, 8 hours, Day 3 prior to dosing (48 hours (+/- 6 hours)) and on Day 7 (168 hours (+/- 6 hours)) or
- Schedule 2: Day 1: End of Infusion, 2 hours, 6 hours, Day 5 prior to dosing (96 hours (+/- 6 hours)) and on Day 7 (168 hours (+/- 6 hours)).

The exact time and date of drug administration and of the PK samples will be documented in the CRF.

10.2 Medical Resource Use

Medical resource use (MRU) data will be collected for all study participants and analyzed by health outcomes (overall survival and response (CR+CRi) for CPX-351 vs. control arms. The MRU data collected in the trial will be used to identify costs associated with planned induction and consolidation treatment and for unplanned medical interventions necessary for patient support. Specific MRU data collected will include but may not be limited to:

- hospitalization nights (general ward and intensive care);
- blood product support (PRBC, Platelets, other);
- non-chemotherapy drugs (anti-infectives, growth factors, etc.); and
- AML chemotherapy (induction vs. consolidation).

11 Statistical Considerations

11.1 Study Overview

This is a randomized phase III study with equal allocation to each of the two treatments: 100 u/m² of CPX-351 (arm A) and standard of care (7+3, arm B). This study is designed to assess the efficacy and confirm the safety of 100 u/m² of CPX-351 compared to the

standard of care (7+3). A total of 300 patients will be accrued and randomized to obtain 270 evaluable patients. This study will use a dynamic allocation procedure to allocate an equal number of patients to each of the treatment regimens. The procedure will balance the marginal distribution of the stratification factors between these treatment regimens (see Section 4.1 for stratification factors).

11.2 Primary and Secondary Endpoints

11.2.1 Primary Endpoint

The primary objective of this study is to compare overall survival (OS), as defined in Section 8.2. All patients who have signed a consent form and have been randomized will be evaluable for overall survival.

11.2.2 Secondary Endpoints

Secondary efficacy endpoints include overall post induction response (CR, CR+CRi) rate, best response (CR, CR+CRi) rate (after completion of the treatment phase), remission duration (relapse-free survival) and event-free survival (EFS) as defined in Section 8.

Additional endpoints also include the rate of morphologic leukemia-free state, the rate of transfer for stem cell transplant and the following safety assessments: Deaths, SAEs, AEs, laboratory tests, vital signs, ECG, and echocardiography. In addition early (by Day 30 and 60) deaths will be monitored.

11.3 Sample Size and Power Justification for Primary Endpoint

The study will accrue 270 evaluable patients (135 per arm). An additional 30 patients (15 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on evaluable patients only and will be referred to as "patients" throughout the remainder of the statistical section. Assuming a uniform recruitment of 135 evaluable patients per year, two years will be required to complete enrollment of 270 patients. Furthermore, patients will be followed until the last patient enrolled has been followed for ≥ 1.2 years. Assuming exponential survival, and a median OS of 0.526 years in the control arm (Arm B), 236 deaths are expected to occur after opening of the study, resulting in a study with 93.7% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 between the two treatment arms. Total time for study completion is approximately 3.2 years.

When the eligibility criteria of the Phase III study is applied to the sAML patients enrolled in the 204 Phase II study a hazard ratio of 0.40 is observed. This study is designed to have 93.7% rather than 90% power for the primary endpoint to assure that the sensitivity analysis, which accounts for the impact of transplant on survival is adequately powered to 90% for the same hazard ratio of 0.635 and the same patient population. Please see Section 11.5.5 for details on this sensitivity analysis.

11.4 Analysis of Primary Endpoint

Efficacy analysis will be performed on an intent to treat basis. A stratified log-rank test will be used to compare the experimental arm (Arm A) to the control arm (Arm B). The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 total eligible patients per year, an accrual period of 2 years, an additional follow-up period of 1.2 years and a median overall survival of 0.526 years, 236 events are expected to occur within 3.2 years after the opening of the study. The number of events is based on the alternative hypothesis. In addition, the distribution of OS in each arm will be estimated using the method of Kaplan-Meier by treatment group. The hazard ratio and OS rates at different time points, along with corresponding confidence intervals will be reported. Exploratory multivariate analyses will be performed to assess the treatment effect adjusting for key prognostic factors using the Cox proportional hazard regression model. This primary efficacy analysis will be performed on the *intent-to-treat population*.

A detailed statistical analysis plan specifying all planned analyses to be performed will be developed for this study before the analyses are conducted.

11.5 Analysis of Secondary Endpoints

Secondary efficacy endpoints include response (CR, CR+CRi) rate, best response (CR, CR+CRi) rate, remission duration (relapse-free survival), and event-free survival (EFS) as defined in Section 8.

In addition, we will perform a sensitivity analysis to account for the impact of transplant on survival (See Section 11.5.5).

All efficacy analyses will be performed on an intent-to-treat basis using the ITT analysis population.

11.5.1 Time dependent endpoints

Time dependent endpoints, such as remission duration and event-free survival (EFS), will be evaluated using a stratified log-rank test to compare the experimental arm to the control arm. In addition, the method of Kaplan-Meier will be used to estimate and display the distribution of these endpoints over time. Exploratory multivariate analyses will be performed to assess the treatment effect adjusting for key prognostic factors using the Cox proportional hazard regression model. Specific subgroup analyses will be performed to assess whether the treatment effect differs according to the stratification factors.

11.5.2 Binary Endpoints

The response (CR, CR+CRi) rate and best response (CR, CR+CRi) rate will be calculated based on the responses achieved as defined in section 8.4. The number of patients who achieve a CR or CRi will be divided by the number of patients in the intent-to-treat analysis population.

Likewise, the rate of achieving a morphologic leukemia-free state will be calculated as the number of patients who develop this state, as defined in section 8.6, divided by all randomized patients who have at least one evaluable post-randomization bone marrow assessment performed on Day14-21 after the last induction.

The rate of stem cell transplant will be calculated by the number of patients starting conditioning treatment for stem cell transplant divided by the number of patients who have received at least one induction course.

The difference in response rate, morphologic leukemia-free rate and rate of transfer for stem cell transplant between the two treatment arms will be calculated using the Mantel-Haenszel test. These comparisons will be stratified by the stratification factors specified in Section 4.1. In addition, multivariate logistic regression analysis will be performed to assess the treatment effect while adjusting for key prognostic factors.

11.5.3 Analysis Populations

All efficacy analyses will be performed on an intent to treat basis using the *Intent-to-treat population* as defined in section 11.7. The analysis for transfer to stem cell transplant will be performed on the *per protocol population* as defined in section 11.7. Finally, the analysis on morphologic leukemia-free state will be performed on the *population* that achieves a morphologic leukemia-free state as defined in section 11.7.4. In addition a sensitivity analysis will be performed on all efficacy endpoints using the *per protocol population*. Further, the MDS subpopulation, consisting of those with MDS by history and patients with MDS by karyotype only; will be analyzed for OS, EFS, CR+CRi, best response, remission duration and 60-day mortality.

11.5.4 Power Considerations for the Secondary Efficacy Endpoints

In the 204 study the observed hazard ratio for event-free survival of the CPX-351 arm versus the 7+3 arm was 0.35 in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. The Phase III trial design with 270 patients total accrued over a period of 2 years with a 1.2 year follow-up yields >99.9% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.35 between arms. These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 74% in the CPX-351 arm and 42% in the 7+3 arm. The Phase III trial design with a total of 270 patients yields 99.99% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 32% in the CPX-351 arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 42%.

11.5.5 Sensitivity Analysis and Power considerations for Sensitivity Analysis

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time of transplant. This analysis will account for the impact of transplant on survival and will

be performed on the ITT population. To minimize bias due to transplant, stratification by risk which includes age (see Section 4.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 270 patients accrued in two years, followed for 1.2 years, median OS in control group 0.526 years. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635.¹⁷ We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 89.9% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm still yields a study with 90.2% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635.

11.6 Safety Analysis

Safety data will be analyzed and reported for all patients in the *safety population* as defined in section 11.7. Safety data will be summarized and will include hematology, coagulation, chemistries, urinalysis, vital signs, ECG, echocardiography and adverse events (AEs). AEs will be coded using the MedDRA coding dictionary. Laboratory values will be summarized both by actual result and by toxicity grade. The maximum grade for each type of toxicity will be recorded and reported for each patient, and frequency tables will be reviewed to determine toxicity patterns.

The laboratory data, vital signs, ECG, and echocardiography will be summarized using descriptive statistics (n, mean, standard deviation, median, min and max) at each scheduled time point. The number and proportion of patients with reported AEs will be tabulated by treatment group.

Early death rates (by Day 30 and 60) will be evaluated separately for each arm by the number of deaths occurring in those time intervals divided by the total number of patients in the respective arm.

All patients will have serum copper levels assessed at baseline prior to the first dose, after the last induction and at Day 150. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels. The proportion of patients with elevated serum copper levels after the end of treatment with CPX-351 or 7+3 will be determined for each treatment arm. Comparisons between arms will be made using the Mantel-Haenszel test. These comparisons will be stratified by the stratification factors specified in Section 4.1.

A Data and Safety Monitoring Board will oversee the conduct of the study. The Board consists of at least two hematologists, one cardiologist, and one statistician. The committee meets at specified intervals and reviews safety data including day 30 and 60 deaths and SAEs. This Board will be responsible for decisions regarding possible termination and/or early reporting of the study.

11.7 Analysis Populations

11.7.1 Intent-to-treat Population

The intent-to-treat population is all patients who have been randomized to the trial. Patients are assigned to treatment arms based on what they were “randomized” to receive. This is the primary efficacy population.

11.7.2 Safety Population:

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin) are in the safety population. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

11.7.3 Per Protocol Population:

These patients are a subset of the intent-to-treat population. The per-protocol population includes all patients who have met inclusion/exclusion criteria and have received at least one dose. The analysis of transfer to stem-cell transplant will be performed on this study population.

11.7.4 Morphologic Leukemia-free State Population

These patients are a subset of the per-protocol population. The morphologic leukemia-free state (MLS) population includes all randomized patients who have met inclusion/exclusion criteria, have received at least one dose and have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction.

11.7.5 Summary of Analysis Populations

Population	OS	EFS	CR/CRi rate*	CR/CRi duration*	MLS	30/60Day Mortality	SAE	Grade >3 AE	Labs
ITT	X	X	X	X					
Per-protocol	X	X	X	X					
MLS			X	X	X				
Safety						X	X	X	X

*includes best response

11.8 Timing of Analyses

An analysis of induction response (CR+CRi) will be performed after all patients have been accrued and completed induction and consolidation treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized,

treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR, CR+CRi) and remission duration will be performed after the endpoint for the primary analysis has occurred.

12 Administrative, Regulatory and Ethical Issues

12.1 Direct Access to Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case report forms, all copies of test results, and study-related regulatory documents [e.g., Informed Consents, Institutional Review Board (IRB)/Ethics Committee (EC) approvals/correspondence, etc.] must be available at all times for regulatory agency inspection and review by the sponsor or its designee. During the periodic site monitoring visits, the source documents will be verified against data entered onto the CRF in order to assure that all data is accurately and completely reflected on the patient's CRF.

12.2 Study Monitoring and Quality Inspections/Audits

This study will be monitored by the sponsor or its designee according to GCP/ICH guidelines. A site visit will be held prior to initiation of patient enrollment. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail at the site visit. Subsequent to patient enrollment, a study site monitor from the sponsor or its designee will review the CRFs and source documents to ensure that the study is conducted according to the protocol and GCP/ICH guidelines. Sponsor's or its designee audit reports will be kept confidential.

To ensure compliance with GCP/ICH guidelines and all applicable regulatory requirements, the sponsor or its designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits or inspections can occur at any time during or after completion of the study. If audits or inspections occur, the Investigator and the Institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The investigator

must promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

12.3 Ethics

This study will be conducted in accordance with local regulations, GCP, ICH guidelines and the Declaration of Helsinki. The Investigator at each site will be responsible for the overall conduct of the clinical trial for the site and will be responsible for ensuring the trial is conducted according to the protocol and all regulatory requirements and IRB/EC regulations.

12.4 Adherence to the Protocol

Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol will be conducted as described. If a change in the conduct is made to eliminate an immediate hazard, the Sponsor and the IRB/EC are notified immediately.

Deviations from the protocol will be considered in two categories, Protocol Violations and Protocol Deviations. Protocol Violations are those patients who are not eligible according to the inclusion/exclusion criteria in effect at the time of randomization. Protocol Deviations are all other non-compliance with the protocol, such as missing or skipped procedures or evaluations, evaluations performed outside given window, incorrect administration of investigational product, etc..

12.5 Protocol Revisions

12.5.1 North America

All revisions must be discussed with, and be prepared by, the Sponsor. If the revision is an Administrative Letter, the investigator should submit it to the IRB/EC for their information. If the revision is an Amendment, it will be signed by the Investigator. The investigator must submit the Amendment to the IRB/EC for review and approval prior to implementation. Documentation of approval signed by the Chairperson or designee of the IRB/EC must be sent to the Sponsor.

If an Amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB/EC for review and approval; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

All revisions will be sent to the national competent authorities in North America.

12.6 Retention of Patient Records and Study Files

CRFs and other reports (e.g., investigator trial files, source documents, original, signed/dated informed consent forms) pertaining to this clinical investigation must be maintained for a minimum of 2 years following written notification by the sponsor of either regulatory approval or discontinuation of the development program. However, the

investigator must obtain the Sponsor's agreement prior to disposal or transfer of responsibility for any study-related records.

12.7 Patient Confidentiality

The sponsor and/or its designee will preserve the confidentiality of all patients taking part in this trial. In the event of patient names inadvertently appearing on the trial documentation, this information will not be entered into the computer database for this trial. Representatives of the sponsor or its designee will seek access to clinical information only after approval to do so has been given by the patient and the relevant authorities. The data from this trial may be used in company publications and submissions to regulatory authorities.

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

What protected health information (PHI) will be collected from patients in this study
Who will have access to that information and why
Who will use or disclose that information

The rights of a research patient to revoke their authorization for use of their PHI:

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is/is not alive) at the end of their scheduled study period.

12.8 Informed Consent

Patients will be required to sign a statement of informed consent that meets the requirements of the US Code of Federal Regulations (21 CFR 50), Canadian regulations, local regulations, ICH guidelines and the IRB/EC of the study center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the study and the date written consent was obtained.

Members of the treating team will review the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and alternative therapies including best supportive care. Patients must be informed that participation in the study is voluntary, he/she may withdraw from the study at any time and withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the study, as well as the efforts to maintain patient confidentiality will also be discussed.

This consent must be witnessed and dated and retained by the Investigator as part of the study records. A copy of the informed consent form must be given to the patient. In the

event the patient is re-screened, the patient is not required to sign another informed consent form unless the patient is re-screened more than 30 days from the previous informed consent form signature date.

If an Experimental Subject's Bill of Rights is applicable in the Investigator's US state, that form must also be prepared and signed by each patient and retained as a part of the required study records. A copy of the Bill of Rights must be given to the patient or the patient's legally authorized representative.

A copy of the IRB approved consent form must be submitted to the Sponsor or its designee prior to shipment of drug supplies to the Investigator. Each patient's signed informed consent must be kept on file by the Investigator for regulatory authority and Sponsor (or its designee) inspection at any time.

For all US sites, the HIPAA Privacy Rule Authorization language must be included in the Informed Consent/authorization form (or a separate authorization document) and approved by the IRB (or Privacy Board). The elements of the HIPAA Privacy Rule Authorization are found in APPENDIX 6: Elements of the HIPAA Privacy Rule Authorization.

The Declaration of Helsinki, as amended, recommendations (2008 version), guiding doctors in clinical research must be signed by the Investigator and returned to the Sponsor or its designee. A copy must also be kept on file by the Investigator. The IRB/EC of an institution must approve the consent form document to be used at that center prior to its local activation; changes to the consent form during the course of the study will also require IRB/EC notification/approval.

The following elements must appear in the consent form: a description of the purpose of the study (indication, that the drug is investigational); potential side effects; potential benefits; study design; voluntary participation; and confidentiality. It is essential that the consent form contain a clear statement that gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the Sponsor and other agencies as necessary.

12.9 Publication Policy

The results of this study will be published. Authorship sequence for the final manuscript, interim publications and abstracts will be decided by the Sponsor in consultation with all investigators. This will generally be decided according to the number of patients accrued. Each contributing center (and participating investigator) will be acknowledged in the final manuscript. In addition, representatives for the Sponsor may be added, as appropriate, as co-authors.

To prevent premature disclosure of proprietary information and to protect the publication rights of other investigators in multicenter trials, the Sponsor requires review of written and oral presentation at least 45 days prior to initial submission to the publishing

authority. If necessary to protect proprietary rights of information to be disclosed in the publication, the Sponsor may request a further 45 day delay in submission for publication, and the investigators agree to make all reasonable efforts to grant such further delay to the Sponsor.

If the investigators have not submitted the results for publication within six months after the completion of the final study report, the Sponsor will have the right to publish. In this case, the investigators will be given two months for review and comment prior to submission to the publisher.

No participant will present data from his/her study site separately from the rest of the study results, unless approved by the other investigators and by the Sponsor.

CPX351.C.PRTCL.00004.V2.3

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14 APPENDIX 1: Patient Evaluation Flow Sheet – Treatment PhaseEach INDUCTION¹ and CONSOLIDATION:

	Day:	Screening	1	2	3	4	5	6	7	10 ±1	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	Weekly ³ ±2	150 ⁸ ±10	End of Phase/Early Term.
Informed Consent ¹		X																
Medical/Leukemia History		X																
Physical Exam		X																
Vital Signs		X									X				X			
ECOG Performance Status		X									X				X			
ECG		X																
Registration & Randomization		X															X	
Hematology		X	X				X		X	X	X	X	X	X	X	X		
Biochemistry		X	X				X		X	X	X	X	X	X	X	X		
Urinalysis		X																
Copper levels		X					X				X				X ⁹		X	
PK sampling ⁷			X				X		X									
Bone Marrow Evaluation		X									X ⁵							
Chest X-ray/Chest CT		X																
Echocardiography/MUGA		X													X ¹⁰		X	
Response Assessment																		
Cytogenetics/Molecular Studies		X																
Adverse Events																		
Concomitant Medications																		
At the time of CR or CRi																		
Assess throughout Induction and Consolidation																		
Assess throughout Induction and Consolidation																		
Treatment Administration	ARM A: CPX-351		X			X			X ²									
	ARM B:																	
OR																		
	Cytarabine		X	X	X	X	X	X ²	X ²	X ²								
	Daunorubicin		X	X	X ²													

¹The first induction may end prematurely if a second induction is necessary, see Section 4.6. The schedule of evaluations for the first induction is followed until the second induction starts, then the evaluations are followed as indicated in the flow sheet, beginning with Day 1²Second inductions and consolidations of ARM A are CPX-351 on Days 1 and 3 and ARM B is 5 days of cytarabine and 2 days of daunorubicin, see Sections 4.6 & 4.7. See Section 7 for an alternative consolidation regimen of intermediate dose cytarabine for patients that exceed 500mg/m² cumulative daunorubicin-equivalent dose³Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared⁴Within 30 days prior to start of screening, if informed consent was collected, 30 days elapse and the patient is still not screened he/she must sign another ICF⁵Required after each induction; (in case the Day 14 bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine effect and need for second induction); as needed thereafter to confirm response/persistence/relapse in second inductions & consolidations⁶Induction(s) only; see Section 8.4.1 for details on when response is assessed.⁷CPX-351 patients will be randomized to one of two PK sampling schedules: See Section 6.2 for the timing of PK draws⁸Day 150 or 45 Days after the last treatment whichever is later⁹After the last induction See Section 9.3¹⁰See Section 9.3, Repeat ECHO/MUGA before the second consolidation if patient exceeds 500mg/m² of cumulative daunorubicin-equivalent doseCONFIDENTIAL
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15 APPENDIX 2: Patient Evaluation Flow Sheet –Follow-up

	Monthly for 1 Year (±10 Days)	Once Years 2-5	Early Termination
Patient status report	x	x	x
Hematology	x		x
Biochemistry	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from randomization, or the initiation of new therapy and/or relapse. (whichever is earliest)		
Copper levels	If elevated copper (>20% above ULN) persists at Day 150 perform monthly until abnormality returns to baseline or until 1 year from randomization.		
Bone Marrow Aspiration/Biopsy	For patients in CR or CRi perform at any time that there is a suspicion of relapse. For patients in CR, perform if peripheral blood counts fall below 1000/ μ L for ANC or 100,000/ μ L for platelets for >1 month or at any time there is suspicion of relapse. For patients in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a patient with a CRi recover to CR levels (\geq 1000/ μ L for ANC or \geq 100,000/ μ L for platelets), perform a bone marrow evaluation within 14 days to confirm CR. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following the initiation of new therapy and or relapse.		
Echocardiography or MUGA scan	If last LVEF treatment phase or Day 150 was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline (\pm 5%) or until 1 year from randomization. Persistent reductions in LVEF of >10% with nadir values below 50% documented at 1 year are considered permanent sequelae.		
Adverse Events/Toxicity	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.		

16 APPENDIX 3: WHO Classification of Secondary Acute Myeloid Leukemia¹⁸

The eligible patient population based on WHO:

Therapy related AML:

Requires more than 20% blood or marrow blasts AND prior cytotoxic therapy for an unrelated disease:

- alkylating agents
- ionizing radiation therapy: large fields including active bone marrow
- topoisomerase II inhibitors
- others: antimetabolites, antitubulin agents

Acute myeloid leukemia with myelodysplasia-related changes:

Requires more than 20% blood or marrow blasts AND any of the following:

1. Previous history of myelodysplastic syndrome (MDS) requires:

Bone marrow evidence of dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryotypes	AND/OR	Unequivocal dysplasia in $< 10\%$ of cell in one or more myeloid cell lines with clonal abnormalities characteristic of MDS ¹
¹ Clonal abnormalities: Unbalanced changes: +8*, -7 or del(7q), -5 or del(5q); del(20q)*, -Y*, i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13) Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); inv(3)(q21q26.2), t(6;9)(p23;q34)		
*If the sole cytogenetic abnormality, also needs morphologic criteria with dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryotypes; all other clonal abnormalities are sufficient for a presumptive diagnosis		

OR

2. With myelodysplastic syndrome-related cytogenetic abnormalities:
- Complex karyotype (defined as 3 or more chromosomal abnormalities).
 - Unbalanced: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
 - Balanced: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34)

AML with a history of CMMoL:

Requires more than 20% blood or marrow blasts AND a history of CMMoL which requires:

- Peripheral blood monocytois $> 1000/\mu\text{L}$
- Absence of Philadelphia chromosome or BCR-ABL1 fusion gene
- In the presence of eosinophilia, absence of rearrangements of PDGFRA or PDGFRB
- Presence of dysplasia in one or more myeloid lineages
- If myelodysplasia is absent/minimal the diagnosis of CMMoL may still be made if the above requirements are met and in addition there is the:
 - presence of acquired clonal cytogenetic or molecular genetic abnormality in hematopoietic cells OR
 - persistence of monocytois for ≥ 3 months and
 - all other causes of monocytois have been excluded
- At diagnosis of CMMoL there are fewer than 20% blasts (myeloblast, monoblast, promonocytes) in peripheral blood and bone marrow.

17 APPENDIX 4: Performance Status – ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

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18 APPENDIX 5: Common Terminology Criteria for Adverse Events V3.0 (CTCAE)

This 72 page document can be obtained as a pdf file from <http://ctep.cancer.gov>.
The publication date is December 12, 2003

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19 APPENDIX 6: Elements of the HIPAA Privacy Rule Authorization

- Written in plain language understandable to the patient or the representative;
- A “specific and meaningful” description of Protected Health Information (PHI) to be used and disclosed;
- The specific identification of the person/class authorized to make the use or disclosure;
- The specific identification of the persons/class to whom the covered entity may make the requested use or disclosure;
- Description of the purpose of the disclosure;
- An expiration date or event (i.e., “no expiration date” for data repository use, or “for the duration of a specific research study” permits use until end of study plus time for wrapping up and reporting);
- A statement of the patient’s right to revoke the authorization and any exceptions to the right to revoke;
- Conditions, if any, on authorization;
- A statement about possible re-disclosures of PHI by the recipient and that the PHI will no longer be protected by the Privacy Rule in the event of such re-disclosures; and
- The signature and date of the patient (or of the patient’s personal representative, along with the personal representative’s authority to act).

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20 APPENDIX 7: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES
FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Available at <http://www.wma.net/en/20activities/10ethics/10helsinki/>)

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21 APPENDIX 8: Anthracyclines Equivalents Guidelines

According to the exclusion criteria patients with a total lifetime anthracycline exposure exceeding the equivalent of 368 mg/m² of daunorubicin (or equivalent) prior to start of study therapy [100 u/m² of CPX-351 contains 44 mg/m² of daunorubicin x 3 doses (1 induction) = 132 mg/m² + 368 mg/m² = 500 mg/m² = maximum allowable limit of daunorubicin from all sources at the end of the 1st induction] are excluded from Protocol CLTR0310-301.

	Conversion factor*
Daunorubicin	1
Doxorubicin	2
Epirubicin	1
Idarubicin	4
Mitoxantrone	4.4

Multiply the number in the second column by the total cumulative dose a patient has received.

For example:

200mg/m² of mitoxantrone x 4.4(conversion factor) = 880mg/m²

This means 200mg/m² of mitoxantrone is equivalent to 880 mg/m² of daunorubicin

*Adapted from Keefe D., Anthracycline-Induced Cardiomyopathy. Seminars in Oncology, Vol 28, No 4, Suppl 12 (August), 2001: pp 2-7

22 APPENDIX 9: Version 2 Summary of Changes

This first amendment of the protocol (Version 2.0) increases the sample size of the study to 300 to provide greater power to the study. This amendment also provides for:

- an optional consolidation schedule for patients that have exceeded 500mg/m² lifetime exposure to daunorubicin or its equivalent
- an additional pharmacokinetic sample
- increase in copper sampling

These additions and other clarifications are outlined below. The amendment also corrects some grammatical and typographical errors that do not change the meaning or intent of the section and therefore are not outlined here.

Protocol Synopsis Page 4, Objectives:

Previously Read:

Primary

- To confirm the efficacy of CPX-351 compared to "7+3" as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.
- To confirm the safety of CPX-351

Secondary

- To confirm the improvement in achievement of morphologic leukemia free state¹
- To confirm post-induction response (CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare pharmacoeconomic differences between the treatment arms

Changed to Read:

Primary

- To confirm the efficacy of CPX-351 compared to "7+3" as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.
-

Secondary

- To confirm the safety of CPX-351
- To confirm the improvement in rate of morphologic leukemia free state¹, post-induction response (CR, CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR, CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare pharmacoeconomic differences between the treatment arms

Protocol Synopsis Page 4, Study Design, last paragraph, first sentence:

Previously Read:

Study enrollment duration is expected to be approximately 20 months.

Changed to Read:

Study enrollment duration is expected to be approximately 2 years.

Protocol Synopsis Page 4, Sample Size:**Previously Read:**

Two hundred forty (240) patients will be randomized with equal allocation between arms to obtain a minimum of 220 evaluable patients: 110 in the CPX-351 arm and 110 in the 7+3 arm.

Changed to Read:

Three hundred (300) patients will be randomized with equal allocation between arms to obtain a minimum of 270 evaluable patients: 135 in the CPX-351 arm and 135 in the 7+3 arm.

Protocol Synopsis Page 6, Dosage Regimen, Second Induction, first sentence:**Previously Read:**

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving >50% reduction in % blasts count on the Day 14 bone marrow assessment.

Changed to Read:

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving >50% reduction in % blasts count on the Day 14 bone marrow assessment, if safe to administer.

Protocol Synopsis Page 6, Dosage Regimen, Consolidation Dosing table,**footnote added:**

*Alternative dosing is available for patients with >500mg/m² of anthracycline exposure, see Section 7.

Protocol Synopsis Page 7, Other Variables and Analysis, PK and Copper paragraphs:**Previously Read:**

PK Sampling for population PK: Patients randomized to CPX-351 are to have samples drawn for population PK. Four samples per patient are taken during the first induction course. CPX-351 patients will be sub-randomized to one of two PK sampling schedules: Schedule 1 Day 1: 45 min, 3 hrs, 8 hrs and prior to dosing on Day 3 (48 hrs (+/- 6 hrs)) or Schedule 2: Day 1: End of Infusion, 2 hrs, 6 hrs and prior to dosing on Day 5 (96 hr (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF.

Serum Copper Sampling: All patients, including those in the control arm, will have serum copper levels assessed at baseline prior to the first dose, after the last induction and at Day 150. The data will be used to assess the variability of serum copper levels in the population as a whole and to determine the proportion of patients with persistently elevated serum copper levels after the end of treatment with CPX-351. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels.

Changed to Read:

PK Sampling for population PK: Patients randomized to CPX-351 are to have samples drawn for population PK. Four samples per patient are taken during the first induction course, all times are relative to the start of Day 1 infusion. CPX-351 patients will be sub-randomized to one of two PK sampling schedules: Schedule 1 Day 1: 45 min, 3 hrs, 8 hrs, Day 3 prior to dosing (48 hrs (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)) or Schedule 2: Day 1: End of Infusion, 2 hrs, 6 hrs, Day 5 prior to dosing (96 hr (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF.

Serum Copper Sampling: All patients, including those in the control arm, will have serum copper levels assessed at baseline prior to the first dose, on Day 5, Day 14, after the last induction dose and at Day 150. The data will be used to assess the variability of serum copper levels in the population as a whole and to determine the proportion of patients with persistently elevated serum copper levels after the end of treatment with CPX-351. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels.

Protocol Synopsis Page 8, Independent Assessments, Data and Safety Monitoring Board, third bullet point:

Previously Read:

- A single assessment of early deaths will be conducted after 60 patients (30 per arm) have been accrued and followed for 60 days.

Changed to Read:

- A single assessment of early deaths will be conducted after 75 patients (37 per arm) have been accrued and followed for 60 days.

Protocol Synopsis Page 8, Statistical Analysis:

Previously Read:

This is a randomized phase III study with equal allocation to each of the two treatments, CPX-351 (arm A) and standard of care (7+3, arm B). A total of 220 evaluable patients (110 patients per arm) will be enrolled in this study. Furthermore, we anticipate an accrual rate of 135 evaluable patients per year. An additional 20 patients (10 in each arm) will be accrued to account for ineligibilities and withdrawal of consent.

Primary Endpoint: The primary objective of this study is to compare overall survival (OS), as defined in section 8.2, in all randomized patients. A median OS of 6 months is anticipated in the control arm (Arm B). Assuming exponential survival, 110 patients per arm results in a study with 94% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.060 between the two treatment arms. The analysis for the primary endpoint will be performed after 190 deaths (86%) have occurred. Assuming exponential survival, uniform recruitment of 135 eligible patients per year, 1.65 years of accrual and 1.2 years of follow-up and a median overall survival of 6 months, 190 events are expected to occur within 2.85 years after the opening of the study.

Changed to Read:

This is a randomized phase III study with equal allocation to each of the two treatments, CPX-351 (arm A) and standard of care (7+3, arm B). A total of 270 evaluable patients (135 patients per arm) will be enrolled in this study. Furthermore, we anticipate an accrual rate of 135 evaluable patients per year. An additional 30 patients (15 in each arm) will be accrued to account for ineligibilities and withdrawal of consent.

Primary Endpoint: The primary objective of this study is to compare overall survival (OS), as defined in section 8.2, in all randomized patients. A median OS of 0.526 years is anticipated in the control arm (Arm B). Assuming exponential survival, 135 patients per arm results in a study with 93.7% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 between the two treatment arms. The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 eligible patients per year, 2 years of accrual and 1.2 years of follow-up and a median overall survival of 0.526 years, 236 events are expected to occur within 3.2 years after the opening of the study.

Section 3.1 Primary Objectives, page 22:

Previously Read:

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 yrs) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.
- To confirm the safety of CPX-351

Changed to Read:

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 yrs) with high risk (secondary) AML. The primary efficacy endpoint will be overall survival.

Section 3.2 Secondary Objectives, Page 22:

Note: this contains additional revisions to match the synopsis.

Previously Read:

- To confirm the improvement in rate of leukemia-free state, response (CR+CRi) rate, remission duration (relapse-free survival), event-free survival and overall best response (CR+CRi) rate following CPX-351
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare Pharmacoeconomic differences between CPX-351 and control

Changed to Read:

- To confirm the safety of CPX-351
- To confirm the improvement in rate of leukemia-free state, post-induction response (CR, CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR, CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population pharmacokinetics of CPX-351 in patients
- To assess and compare Pharmacoeconomic differences between CPX-351 and control

Section 4.4 Sample Size, page 26:

Previously Read:

Two-hundred forty (240) patients will be randomized to obtain approximately 220 evaluable patients. Equal numbers of patients will be randomized to CPX-351 (Arm A) or cytarabine and daunorubicin (Arm B, 7+3).

Changed to Read:

Three hundred (300) patients will be randomized to obtain approximately 270 evaluable patients. Equal numbers of patients will be randomized to CPX-351 (Arm A) or cytarabine and daunorubicin (Arm B, 7+3).

Section 4.6 Repeat of Induction, first sentence, page 26:**Previously Read:**

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving >50% reduction in % blasts count on the Day 14 bone marrow assessment.

Changed to Read:

A second induction is highly recommended for any patient with documented reduction in leukemia burden and is mandatory for patients achieving >50% reduction in % blasts count on the Day 14 bone marrow assessment, if safe to administer.

Section 4.7 Consolidation Therapy, page 27, added fourth paragraph:

A minority of patients will have prior anthracycline exposure and for these patients only, study treatment may push the cumulative exposure to anthracycline above 500 mg/m² (calculated as daunorubicin equivalents, See APPENDIX 8: Anthracyclines Equivalents Guidelines). For patients who exceed 500 mg/m², additional cardiac monitoring will be performed prior to all subsequent courses of anthracycline-containing therapy with ECHO/MUGA. Patients must be confirmed to have >50% LVEF without evidence of ≥10% decrease in LVEF compared to baseline values. If there is any doubt about the cardiac safety of additional study therapy, investigators may contact the sponsor. In addition, investigators treating patients with cumulative anthracycline exposure ≥500 mg/m² will have the option to use an alternate consolidation regimen of intermediate dose cytarabine, 1.5 g/m² BID on Days 1, 3 and 5 (6 doses). Contact the sponsor prior to initiating this optional consolidation regimen.

For patients with less than 500 mg/m² cumulative anthracycline exposure, including study treatment, who have a >10% absolute decrease in LVEF to less than 50%, may receive the alternate consolidation regimen of intermediate dose cytarabine as described above.

Section 4.11 Data and Safety Monitoring Board, page 28, third bullet point:**Previously Read:**

- Conduct a single interim analysis after 60 patients (30 per arm) have been evaluated for induction mortality with early stop rules. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB.

Changed to Read:

- Conduct a single interim analysis after 75 patients (37 per arm) have been evaluated for induction mortality with early stop rules. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB.

Section 5.2 Withdrawal of Patients, page 31, second paragraph:**Previously Read:**

During any phase of the study, if a patient requests to stop treatment and/or follow-up, the patient will be discontinued and no further information will be collected. The patient will be classified as withdrawal of consent. Any patient that dies on or before Day 7 will be replaced.

Changed to Read:

During any phase of the study, if a patient requests to stop treatment and/or follow-up, the patient will be discontinued and no further information will be collected. The patient will be classified as withdrawal of consent. Any patient that dies on or before Day 7 will be included in the intent-to-treat analysis but will also be replaced to ensure adequate study power.

Section 6.1 Pre-treatment Evaluations table, Molecular Studies, Page 33:**Previously Read:**

Molecular Studies	Central laboratory evaluation of CEBPA, FLT3, and NPM1	Within 3 months prior to randomization: patients may be randomized and treated prior to receiving the results of molecular tests
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Changed to Read:

Molecular Studies	Central or local laboratory evaluation of CEBPA, FLT3, and NPM1	Within 3 months prior to randomization: patients may be randomized and treated prior to receiving the results of molecular tests
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Section 6.2 Evaluations during Treatment Phase table, PK Sampling, Copper, Cytogenetic Studies and Diagnostic Imaging, Page 34 & 35:**Previously Read:**

PK sampling	Plasma concentrations for cytarabine and daunorubicin and metabolites (performed by bioanalytical laboratory)	CPX-351 patients will be sub-randomized to one of two PK sampling schedules: <u>Schedule 1:</u> Day 1: 45 min, 3 hrs, 8 hrs, prior to dosing on Day 3 (48 hrs (+/- 6 hrs)) or <u>Schedule 2:</u> Day 1: End of Infusion, 2 hrs, 6 hrs, prior to dosing on Day 5 (96 hr (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF. Four samples are collected from each patient randomized to CPX-351.
Copper levels	Serum Copper (performed by a central laboratory)	After the last induction that the patient receives; See Section 9.4.1 for details

Cytogenetics Molecular Studies	Cytogenetics (performed locally) Molecular Studies (performed by a central laboratory)	Required in patients with a CR or CRi with positive baseline findings (perform at the time of bone marrow assessment for CR or CRi). Optional in patient with normal findings at baseline
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	After the last induction that the patient receives; See Section 9.3 for details

Changed to Read:

PK sampling	Plasma concentrations for cytarabine and daunorubicin and metabolites (performed by bioanalytical laboratory)	CPX-351 patients will be sub- randomized to one of two PK sampling schedules during the first induction only, all times are relative to the start of Day 1 infusion: <u>Schedule 1:</u> Day 1: 45 min, 3 hrs, 8 hrs, Day 3 prior to dosing (48 hrs (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)) or <u>Schedule 2:</u> Day 1: End of Infusion, 2 hrs, 6 hrs, Day 5 prior to dosing (96 hr (+/- 6 hrs)) and on Day 7 (168 hrs (+/- 6 hrs)). The exact time and date of drug administration and of the PK samples will be documented in the CRF. Four samples are collected from each patient randomized to CPX-351.
Copper levels	Serum Copper (performed by a central laboratory)	Induction 1: Day 5, (For Arm A: 10 minutes after completion of the infusion, Arm B any time on Day 5), Day 14; and after the last induction that the patient receives; See Section 9.4.1 for details
Cytogenetics Molecular Studies	Cytogenetics (performed locally) Molecular Studies (performed locally or by the central laboratory)	Required in patients with a CR or CRi with positive baseline findings (perform at the time of bone marrow assessment for CR or CRi). Optional in patients with normal baseline cytogenetics/molecular studies.
Diagnostic Imaging	Echocardiography or MUGA scan (sent to a central laboratory)	After the last induction that the patient receives and for patients with anthracycline exposure exceeding 500 mg/m ² prior to every course of daunorubicin-containing treatment; See Section 9.3 for details

Section 6.5 Evaluations during Follow-up Phase, Diagnostic Imaging page**36:****Previously Read:**

Diagnostic Imaging	Echocardiography or MUGA	If last LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline or until 1 year from randomization. Persistent reductions in LVEF of >10% and failing below 50% lasting >1 year are considered permanent sequelae.
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Changed to Read:

Diagnostic Imaging	Echocardiography or MUGA	If last treatment phase or the day 150 LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline \pm 5% or until 1 year from randomization. Persistent reductions in LVEF of >10% with nadir values below 50% documented at 1 year are considered permanent sequelae.
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Section 7.0 Drug Administration, added optional consolidation, page 37

Optional Consolidations only for patients with ≥ 500 mg/m² daunorubicin equivalent exposure:

Arm	Agent	Dose	Route	Duration	Schedule
A/B	Cytarabine	1.5 g/m ² /BID	IV	90 minutes	Days 1, 3 and 5

Section 8.5 Remission Duration, last sentence, page 44:**Previously Read:**

For patients whose best response is upgraded from CRi to CR, remission duration will be calculated from date of CRi to date of relapse or death.

Changed to Read:

For patients whose best response is upgraded from CRi to CR, remission duration for CR+CRi analyses will be calculated from date of CRi to date of relapse or death.

Section 9.2.2 Definition of a Serious Adverse Event, fourth paragraph, page 45:**Previously Read:**

Exceptions to the definition of SAE are uncomplicated febrile neutropenia and grade 1-3 bleeding events (with or without platelet transfusions). These events, as they are common and expected in this patient population will NOT be reported as SAEs, but as AEs only. Hospitalizations for routine procedures, investigations and chemotherapy administration are NOT considered SAEs in this protocol.

Changed to Read:

Exceptions to the definition of SAE include hospitalizations due to uncomplicated febrile neutropenia, grade 1-3 bleeding events (with or without platelet transfusions) and hospitalizations due to disease progression. These events, as they are common and expected in this patient population will NOT be reported as

SAEs, but as AEs only. Hospitalizations for routine procedures, investigations and chemotherapy administration are NOT considered SAEs in this protocol.

Section 9.3 Cardiac Toxicity Monitoring, added third time point: page 47:

- 3) Prior to every course of daunorubicin-containing treatment after patient exceeds 500 mg/m² daunorubicin equivalent exposure (including study treatment).

Section 9.4.1 Copper Assessment, time points and last paragraph, page 47:

Previously Read:

- 1) Pre-Treatment
- 2) after the LAST induction that the patient receives
 - a. Responding patients after one or two inductions are assessed 30-45 days after the start of the last induction or before the start of consolidation, whichever is later
 - b. Non-responding patients will be assessed prior to the start of salvage therapy or 30-45 days after the start of the last induction if salvage treatment is not given.
- 3) Day 150 or 45 days from last treatment whichever is later
 - a. ALL patients must have a serum copper assessment 150 days (\pm 10 days) from date of randomization. This is required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 4) Follow-up Period
 - a. If elevated copper (20% above ULN) persists at Day 150, perform monthly until abnormality returns to baseline or 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

Copper data will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection and processing and communication of results will be provided in a separate laboratory manual.

Changed to Read:

- 1) Pre-Treatment
- 2) Induction 1: Day 5 (10 minutes after completion of infusion for Arm A patients; any time on Day 5 for Arm B patients)
- 3) Induction 1: Day 14
- 4) after the LAST induction that the patient receives
 - a. Responding patients after one or two inductions are assessed 30-45 days after the start of the last induction or before the start of consolidation, whichever is later

- b. Non-responding patients will be assessed prior to the start of salvage therapy or 30- 45 days after the start of the last induction if salvage treatment is not given.
- 5) Day 150 or 45 days from last treatment whichever is later
 - a. ALL patients must have a serum copper assessment 150 days (± 10 days) from date of randomization. This is required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.
- 6) Follow-up Period
 - a. If elevated copper (20% above ULN) persists at Day 150, perform monthly until abnormality returns to baseline or until 1 year, whichever comes first. These evaluations are required even if patients have discontinued treatment for persistent or relapsed disease and have started salvage therapy or were transferred for HSCT.

Copper data will be obtained via a central laboratory. Investigators will be provided kits for the collection of specimens and for sending the samples to the laboratory. Data generated by the laboratory will be incorporated into the case report form database prior to the primary endpoint analysis. Specifics about the specimen collection and processing and communication of results will be provided in a separate laboratory manual. At the end of the study the percentage of patients with persistently elevated serum copper levels and the duration of elevated copper levels will be analyzed.

Section 11.0 Pharmacokinetics, added second paragraph, page 49:

Patients randomized to CPX-351 are to have samples drawn for population PK. Five samples per patient are taken during the first induction course. All times are relative to the start of Day 1 infusion. CPX-351 patients will be sub-randomized to one of two PK sampling schedules:

- **Schedule 1:** Day 1: 45 min, 3 hours, 8 hours, Day 3 prior to dosing (48 hours (± 6 hours)) and on Day 7 (168 hours (± 6 hours)) or
- **Schedule 2:** Day 1: End of Infusion, 2 hours, 6 hours, Day 5 prior to dosing (96 hours (± 6 hours)) and on Day 7 (168 hours (± 6 hours)).

The exact time and date of drug administration and of the PK samples will be documented in the CRF.

Section 11.1 Study Overview, third sentence, page 50:

Previously Read:

A total of 240 patients will be accrued and randomized to obtain 220 evaluable patients.

Changed to Read:

A total of 300 patients will be accrued and randomized to obtain 270 evaluable patients.

Section 11.3 Sample Size and Power Justifications for Primary Endpoint, page 50:**Previously Read:**

The study will accrue 220 evaluable patients (110 per arm). An additional 20 patients (10 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on evaluable patients only and will be referred to as "patients" throughout the remainder of the statistical section. Assuming a uniform recruitment of 135 evaluable patients per year, years will be required to complete enrollment of 220 patients. Furthermore, patients will be followed until the last patient enrolled has been followed for ≥ 1.2 years. Assuming exponential survival, and a median OS of 6 months in the control arm (Arm B), 190 deaths are expected to occur after opening of the study, resulting in a study with 94% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.6 between the two treatment arms. Total time for study completion is approximately 2.85 years.

A hazard ratio of 0.41 was observed in the 204 study for sAML patients. To approximate the hazard ratio to be expected in the Phase III study, we assumed one half the efficacy observed in Phase II which would require a sample size sufficient to detect a hazard ratio of approximately 0.060. This study is designed to have 94% rather than 90% power for the primary endpoint to assure that the sensitivity analysis which accounts for potential early drop-outs due to transplant is adequately powered to 90% for the same hazard ratio of 0.6 and the same patient population. Please see Section 11.5.5 for details on this sensitivity analysis.

Changed to Read:

The study will accrue 270 evaluable patients (135 per arm). An additional 30 patients (15 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on evaluable patients only and will be referred to as "patients" throughout the remainder of the statistical section. Assuming a uniform recruitment of 135 evaluable patients per year, two years will be required to complete enrollment of 270 patients. Furthermore, patients will be followed until the last patient enrolled has been followed for ≥ 1.2 years. Assuming exponential survival, and a median OS of 0.526 years in the control arm (Arm B), 236 deaths are expected to occur after opening of the study, resulting in a study with 93.7% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 between the two treatment arms. Total time for study completion is approximately 3.2 years.

When the eligibility criteria of the Phase III study is applied to the sAML patients enrolled in the 204 Phase II study a hazard ratio of 0.40 is observed. This study is designed to have 93.7% rather than 90% power for the primary endpoint to assure that the sensitivity analysis, which accounts for the impact of transplant on survival is adequately powered to 90% for the same hazard ratio of 0.635 and the

same patient population. Please see Section 11.5.5 for details on this sensitivity analysis.

Section 11.4 Analysis of Primary Endpoint, third and fourth sentences, page 51:

Previously Read:

The analysis for the primary endpoint will be performed after 190 deaths (86%) have occurred. Assuming exponential survival, uniform recruitment of 135 total eligible patients per year, an accrual period of 1.65 years, an additional follow-up period of 1.2 years and a median overall survival of 6 months, 190 events are expected to occur within 2.85 years after the opening of the study.

Changed to Read:

The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 total eligible patients per year, an accrual period of 2 years, an additional follow-up period of 1.2 years and a median overall survival of 0.526 years, 236 events are expected to occur within 3.2 years after the opening of the study.

Section 11.5 Analysis of Secondary Endpoints, second paragraph, page 51:

Previously Read:

In addition, we will perform a sensitivity analysis to account for patients transferred to HSCT (See Section 11.5.5).

Changed to Read:

In addition, we will perform a sensitivity analysis to account for the impact of transplant on survival (See Section 11.5.5).

Section 11.5.4 Power Considerations for Secondary Efficacy Endpoints, page 53:

Previously Read:

In the 204 study the observed hazard ratio for event-free survival of the 7+3 arm versus the CPX-351 arm was 1.79 (0.56) in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. This trial design with 220 patients total accrued over a period of 1.65 years with a 1.2 year follow-up yields 99% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 1.79 (0.56) between arms. The same trial design yields 94% power (with a one-sided alpha of 0.025) to detect a hazard ratio of 1.6. These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 56% in the CPX-351 arm and 32% in the 7+3 arm. This trial design with a total of 220 patients yields 94% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 24% in the CPX-351

arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 32%.

Changed to Read:

In the 204 study the observed hazard ratio for event-free survival of the CPX-351 arm versus the 7+3 arm was 0.35 in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. The Phase III trial design with 270 patients total accrued over a period of 2 years with a 1.2 year follow-up yields >99.9% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.35 between arms. These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 74% in the CPX-351 arm and 42% in the 7+3 arm. The Phase III trial design with a total of 270 patients yields 99.99% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 32% in the CPX-351 arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 42%.

Section 11.5.5 Sensitivity Analysis and Power Considerations for Sensitivity Analysis, page 53:

Previously Read:

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time of transplant. This analysis will account for early drop-out due to transplant and will be performed on the ITT population. To minimize bias due to transplant, stratification by risk which includes age (see Section 4.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 220 patients accrued in 1.65 years, followed for 1.2 years, median OS in control group 6 months. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60.¹⁷ We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60.

Changed to Read:

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time of transplant. This analysis will account for the impact of transplant on survival and will be performed on the ITT population. To minimize bias due to transplant, stratification by risk which includes age (see Section 4.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 270 patients accrued in two years, followed for 1.2 years, median OS in control group 0.526 years. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635.¹⁷ We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 89.9% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm still yields a study with 90.2% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635.

Section 11.7.2 Safety Population, page 54:

Previously Read:

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin) and have at least one post-baseline safety follow-up. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

Changed to Read:

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin) are in the safety population. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

Section 11.8 Timing of Analyses, page 55:

Previously Read:

An analysis of induction response (CR+CRi) and 60-day death rate will be performed approximately 90-120 days after the start of treatment of the last randomized patient, which is after all patients have been accrued, treated and recovered from induction treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of

this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized, treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR+CRi) and remission duration will be performed after the endpoint for the primary analysis has occurred.

Changed to Read:

An analysis of induction response (CR+CRi) will be performed after all patients have been accrued and completed induction and consolidation treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized, treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR, CR+CRi) and response duration will be performed after the endpoint for the primary analysis has occurred.

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Section 14.0 Patient Evaluation Flow Sheet- Treatment Phase, Page 62, Currently Reads:Each INDUCTION¹ and CONSOLIDATION:

Day:	Screening	1	2	3	4	5	6	7	10 ±1	14 ±2	21 ±2	28 ±2	35 ±2	42± 2	Weekly ³ ±2	150 ⁸ ±10	End of Phase/Early Term.
Informed Consent ⁴	x																
Medical/Leukemia History	x																
Physical Exam	x									x				x			x
Vital Signs	x									x				x			x
ECOG Performance Status	x																x
ECG	x																x
Registration & Randomization	x															x	
Hematology	x	x		x		x		x	x	x	x	x	x	x			x
Biochemistry	x	x		x		x		x	x	x	x	x	x	x			x
Urinalysis	x																
Copper levels	x													x ⁹			
PK sampling ⁷	x	x		x		x										x	
Bone Marrow Evaluation	x									x ⁵		As needed to confirm response/persistence					
Chest X-ray/Chest CT	x																
Echocardiography/MUGA	x																
Response Assessment																	
Cytogenetics/Molecular Studies	x																
Adverse Events																	
Concomitant Medications																	
Treatment Administration	ARM A: CPX-351	x		x		x ²											
	OR																
	ARM B: Cytarabine Daunorubicin	x	x	x	x	x	x ²	x ²	x ²	x ²							

¹The first induction may end prematurely if a second induction is necessary, see Section 4.6. The schedule of evaluations for the first induction is followed until the second induction starts, then the evaluations are followed as indicated in the flow sheet, beginning with Day 1²Second inductions and consolidations of ARM A are CPX-351 on Days 1 and 3 and ARM B is 5 days of cytarabine and 2 days of daunorubicin, see Sections 4.6 & 4.7³Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared⁴Within 30 days prior to start of screening, if informed consent was collected, 30 days elapse and the patient is still not screened he/she must sign another ICF⁵Required after each induction on Day 14-21; (in case the Day 14 bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine effect and need for second induction); as needed thereafter to confirm response/persistence/relapse in second inductions & consolidations⁶Induction(s) only; see Section 8.4.1 for details on when response is assessed.⁷CPX-351 patients will be randomized to one of two PK sampling schedules: See Section 6.2 for the timing of PK draws⁸Day 150 or 45 Days after the last treatment whichever is later⁹After the last induction See Sections 9.3 & 9.4.1

Section 14.0 Patient Evaluation Flow Sheet- Treatment Phase, Page 62, Changed to Read:Each INDUCTION¹ and CONSOLIDATION:

Day:	Screening	1	2	3	4	5	6	7	10 ±1	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	Weekly ³ ±2	150 ⁸ ±10	End of Phase/Early Term.
Informed Consent ⁴	x																
Medical/Leukemia History	x																
Physical Exam	x									x							
Vital Signs	x									x				x			
ECOG Performance Status	x													x			
ECG	x																
Registration & Randomization	x															x	
Hematology	x	x		x					x	x	x	x	x	x			
Biochemistry	x	x		x					x	x	x	x	x	x			
Urinalysis	x																
Copper levels	x								x								
PK sampling ⁷	x	x		x				x								x	
Bone Marrow Evaluation	x									x ⁵							
Chest X-ray/Chest CT	x																
Echocardiography/MUGA	x																x
Response Assessment																	
Cytogenetics/Molecular Studies	x																
Adverse Events																	
Concomitant Medications																	
Treatment Administration	ARM A: CPX-351	x		x		x ²											
	ARM B:																
	Cytarabine	x	x	x	x	x	x ²	x ²									
	Daunorubicin	x	x	x ²													

OR

- ¹The first induction may end prematurely if a second induction is necessary, see Section 4.6. The schedule of evaluations for the first induction is followed until the second induction starts, then the evaluations are followed as indicated in the flow sheet, beginning with Day 1
- ²Second inductions and consolidations of ARM A are CPX-351 on Days 1 and 3 and ARM B is 5 days of cytarabine and 2 days of daunorubicin, see Sections 4.6 & 4.7. See Section 7 for an alternative consolidation regimen of intermediate dose cytarabine for patients that exceed 500mg/m² cumulative daunorubicin-equivalent dose
- ³Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared
- ⁴Within 30 days prior to start of screening, if informed consent was collected, 30 days elapse and the patient is still not screened he/she must sign another ICF
- ⁵Required after each induction on Day 14-21; (in case the Day 14 bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine effect and need for second induction); as needed thereafter to confirm response/persistence/relapse in second inductions & consolidations
- ⁶Induction(s) only; see Section 8.4.1 for details on when response is assessed.
- ⁷CPX-351 patients will be randomized to one of two PK sampling schedules: See Section 6.2 for the timing of PK draws
- ⁸Day 150 or 45 Days after the last treatment whichever is later
- ⁹After the last induction See Section 9.3
- ¹⁰See Section 9.3, Repeat ECHO/MUGA before the second consolidation if patient exceeds 500mg/m² of cumulative daunorubicin-equivalent dose

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23 APPENDIX 10: Version 2.2 Summary of Changes

This administrative amendment of the protocol (Version 2.2) changes:

- The address of Celator Pharmaceuticals, Inc.
- The source of daunorubicin for Arm B. The sponsor may now provide daunorubicin in the event of a national shortage
- Since the study is only being conducted in the US and Canada, all references to EU sites, EU guidelines and EU drug supply were removed

Protocol Cover Page 1, Celator address:

Previously Read:

[REDACTED]

Changed to Read:

[REDACTED]

Protocol Cover Page 1, Medical Monitor address:

Previously Read:

[REDACTED]

Changed to Read:

[REDACTED]

ABBREVIATIONS, page 9:

Removed:

EU European Union

Section 2.4 Product Label, page 18:

Previously Read:

CPX-351 (cytarabine:daunorubicin) LIPOSOME FOR INJECTION 100 units/Vial
Each unit contains 1.0 mg ($\pm 10\%$) Cytarabine and 0.44 mg ($\pm 10\%$) Daunorubicin (base) in liposomes containing DSPC, DSPG and cholesterol. Also contains copper as copper gluconate, triethanolamine and sucrose.

Store refrigerated at 5°C ($\pm 3^\circ\text{C}$) in an upright position.

FRAGILE: Do not drop

Caution: New Drug – Limited by Federal Law to Investigational Use

Manufactured for

Celator Pharmaceuticals, Inc., [REDACTED]

Lot # _____

Expiration Date: _____

Changed to Read:

CPX-351 (cytarabine:daunorubicin) LIPOSOME FOR INJECTION

100 units/Vial

Each unit contains 1.0 mg ($\pm 10\%$) Cytarabine and 0.44 mg ($\pm 10\%$) Daunorubicin (base) in liposomes containing DSPC, DSPG and cholesterol. Also contains copper as copper gluconate, triethanolamine and sucrose.

Store refrigerated at 5°C ($\pm 3^\circ\text{C}$) in an upright position.

FRAGILE: Do not drop

Caution: New Drug – Limited by Federal Law to Investigational Use

Manufactured for

Celator Pharmaceuticals, Inc., [REDACTED]

Lot # _____

Expiration Date: _____

Section 7.1.2.1 Control Arm Drug Sourcing, page 38:

Previously Read:

The drug products that may be used for the control arm will be sourced by the investigational site. Cytarabine and daunorubicin are approved in the US, Canada and EU and will be obtained from the appropriate market (US for investigational sites in the US, Canadian for sites in Canada, EU country for sites in EU). If for any reason, drug supplies for cytarabine or daunorubicin are or might be unavailable or insufficient to complete a treatment cycle, contact the sponsor as soon as possible: Telephone: [REDACTED] or fax: [REDACTED] or email [REDACTED]

Changed to Read:

In general, the drug products that may be used for the control arm will be sourced by the investigational site. Cytarabine and daunorubicin are approved in the US and Canada and will be obtained from the appropriate market (US for investigational sites in the US, Canadian for sites in Canada). If for any reason, drug supplies for cytarabine or daunorubicin are unavailable or insufficient to complete all potential inductions and consolidations for a particular patient, contact the sponsor as soon as possible: Telephone: [REDACTED] or fax: [REDACTED] or email [REDACTED]

For as long as daunorubicin is listed on FDA's current drug shortage index and if daunorubicin cannot be obtained by the clinical site, Celator will provide daunorubicin. Celator will provide daunorubicin as Cerubidine[®], sourced from Canada and manufactured in Belgium, meeting USP specifications. Cerubidine will be provided on a per patient basis until US commercial supplies are available.

Section 9.2.4 Reporting Serious Adverse Events to Regulatory Agencies and Review Boards, page 47:

Previously Read:

The need for an expedited report to regulatory authorities will be determined by the Sponsor's Medical Monitor. All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the applicable regulatory authority (FDA in the US and to Health Canada in Canada). The Sponsor will notify investigators of all such SAEs and these reports must be submitted by the investigators to the IRB/EC. In Europe, these SAEs will be submitted to the national competent authorities, EudraVigilance and to ECs according to national regulations.

Changed to Read:

The need for an expedited report to regulatory authorities will be determined by the Sponsor's Medical Monitor. All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the applicable regulatory authority (FDA in the US and to Health Canada in Canada). The Sponsor will notify investigators of all such SAEs and these reports must be submitted by the investigators to the IRB/EC.

Section 12.2 Study Monitoring and Quality Inspections/Audits, page 57:

Previously Read:

This study will be monitored by the sponsor or its designee according to GCP/ICH guidelines and EU legislation. A site visit will be held prior to initiation of patient enrollment. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail at the site visit. Subsequent to patient enrollment, a study site monitor from the sponsor or its designee will review the CRFs and source documents to ensure that the study is conducted according to the protocol and GCP/ICH guidelines and EU legislation. Sponsor's or its designee audit reports will be kept confidential.

To ensure compliance with GCP/ICH guidelines and EU legislation and all applicable regulatory requirements, the sponsor or its designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits or inspections can occur at any time during or after completion of the study. If audits or inspections occur, the Investigator and the Institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The investigator must promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

Changed to Read:

This study will be monitored by the sponsor or its designee according to GCP/ICH guidelines. A site visit will be held prior to initiation of patient enrollment. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail at the site visit. Subsequent to patient enrollment, a study site monitor from the sponsor or its designee will review the CRFs and source documents to ensure that the study is conducted according to the protocol and GCP/ICH guidelines. Sponsor's or its designee audit reports will be kept confidential.

To ensure compliance with GCP/ICH guidelines and all applicable regulatory requirements, the sponsor or its designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits or inspections can occur at any time during or after completion of the study. If audits or inspections occur, the Investigator and the Institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The investigator must promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

Section 12.3 Ethics, page 57:

Previously Read:

This study will be conducted in accordance with local regulations, EU legislation, GCP, ICH guidelines and the Declaration of Helsinki. The Investigator at each site will be responsible for the overall conduct of the clinical trial for the site and will be responsible for ensuring the trial is conducted according to the protocol and all regulatory requirements and IRB/EC regulations.

Changed to Read:

This study will be conducted in accordance with local regulations, GCP, ICH guidelines and the Declaration of Helsinki. The Investigator at each site will be responsible for the overall conduct of the clinical trial for the site and will be responsible for ensuring the trial is conducted according to the protocol and all regulatory requirements and IRB/EC regulations.

Section 12.5.2 Europe, page 58:

Paragraph was deleted:

If the revision is substantial (i.e. likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial or if they are otherwise significant) an amendment application must be submitted to the Ethics Committee and the national competent authorities.

Section 12.8 Informed Consent, first paragraph, page 59:

Previously Read:

Patients will be required to sign a statement of informed consent that meets the requirements of the US Code of Federal Regulations (21 CFR 50), Canadian regulations, European Community and European Union National Legislation, local regulations, ICH guidelines and the IRB/EC of the study center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the study and the date written consent was obtained.

Changed to Read:

Patients will be required to sign a statement of informed consent that meets the requirements of the US Code of Federal Regulations (21 CFR 50), Canadian regulations, local regulations, ICH guidelines and the IRB/EC of the study center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the study and the date written consent was obtained.

Section 12.8 Informed Consent, seventh paragraph, page 60:

Paragraph was deleted:

For all European Union sites the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data must be referred to http://www.cdt.org/privacy/eudirective/EU_Directive_.html#HD_NM_12).

24 APPENDIX 11: Version 2.3 Summary of Changes

This administrative amendment of the protocol (Version 2.3) changes the Serious Adverse Event reporting requirements to conform with FDA regulations without exception according to 21 CFR 312.32. All events that result in hospitalization must now be reported to the sponsor.

Section 9.2.2 Definition of a Serious Adverse event, Third paragraph, page 46:

Paragraph was deleted:


Exceptions to the definition of SAE include hospitalizations due to uncomplicated febrile neutropenia, grade 1-3 bleeding events (with or without platelet transfusions) and hospitalizations due to disease progression. These events, as they are common and expected in this patient population will NOT be reported as SAEs, but as AEs only. Hospitalizations for routine procedures, investigations and chemotherapy administration are NOT considered SAEs in this protocol.

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Celator Statistical Analysis Plan

Full Title of Study	Phase III, multicenter, randomized, trial of CPX-351 (Cytarabine: Daunorubicin) liposome injection versus cytarabine and daunorubicin in patients 60-75 years of age with untreated high risk (secondary) AML.
Protocol Number	CLTR0310-301
IND Reference Number	72,939
Date of Plan	May 22, 2012
Version	1.0
Sponsor Name	Celator Pharmaceuticals, Inc.
Sponsor Address	

Approvals

Printed Name	Signature	Date
		

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1.0 List of Abbreviations

Abbreviation	Full Term
7+3	Seven days of continuous infusion of cytarabine at 100 mg/m ² /day and three days of daunorubicin at 60 mg/m ² /day
AE	Adverse Event
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
BSA	Body Surface Area
CMMoL	Chronic Myelomonocytic Leukemia
CPX-351	CPX-351 (cytarabine: daunorubicin) Liposome Injection
CR	Complete Response
CRF	Case Report Form
CRi	Complete Response with incomplete hematologic recovery
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
HSCT	Hematopoietic Stem Cell Transplantation
ITT	Intent-to-treat
m ²	square meters
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
μL	microliter(s)
MLS	Morphologic Leukemia-free State
OS	Overall Survival
PD	Persistent Disease

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PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
t-AML	Therapy-related AML
WHO	World Health Organization

2.0 Introduction

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the study entitled: “Phase III, multicenter, randomized, trial of CPX-351 (Cytarabine: Daunorubicin) liposome injection versus cytarabine and daunorubicin in patients 60-75 years of age with untreated high risk (secondary) AML.”

The purpose of this document is to ensure the credibility of the study outcomes by pre-specifying the statistical approaches and data handling conventions for key analyses. This plan will focus on the analysis of the primary endpoints, which are overall survival (OS) and the safety of CPX-351, and the secondary endpoints, which are response, event-free survival (EFS), additional CPX-351 safety measures, pharmacokinetics (PK), and pharmacoeconomics. The primary analyses of all endpoints will be described, the populations for analysis defined, and all of the rules specified for “data handling” relevant to undertaking the key analyses.

Some assumptions in this analysis plan are based on a prior Phase II study, Protocol CLTR0308-204 (“Study 204”), which enrolled newly diagnosed AML patients 60-75 years of age.

3.0 Study Objectives and Endpoints

3.1 Overview of Study

This study is an open-label, randomized Phase III study, where newly diagnosed AML patients (including t-AML, AML in patients with a history of MDS or CMMoL, and de novo AML in patients with specific adverse karyotypic changes (per WHO definitions)) are randomized with equal allocation to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). A total of 240 patients will be accrued and randomized to obtain 220 evaluable patients. Patients are stratified by age and AML subtype at randomization to balance these prognostic factors across treatment arms. This study will use a dynamic allocation procedure to allocate an equal

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number of patients to each of the treatment regimens. The procedure will balance the marginal distribution of the stratification factors between these treatment regimens.

3.1.1 Stratification and Randomization Scheme

At registration, patients will be randomized to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). Only patients determined to be eligible following a pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow) and confirmation of secondary AML by WHO criteria will be randomized (Appendix 1.) Patients will be stratified on the following factors:

Strata	
Age	Age 60-69 years OR Age 70-75
AML Type	<ul style="list-style-type: none">• Therapy-related AML: t-AML• MDS transformed to AML with prior HMA treatment: _{MDS}AML• MDS transformed to AML without prior HMA treatment: _{MDS}AML• CMMoL transformed to AML: _{CMMoL}AML• De novo AML with MDS karyotype: _{de novo}AML

3.1.2 Dynamic Randomization Algorithm

A dynamic balancing randomization algorithm will be used to ensure that the assignment of treatments is balanced across all the stratification factors. This procedure balances the marginal distribution of the stratification factors between these treatment regimens. The approach used is based on the method described by Pocock and Simon (Pocock and Simon, 1975).

3.2 Study Objectives: Primary

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 years) with secondary AML. The primary efficacy endpoint will be OS.
- To confirm the safety of CPX-351

3.3 Study Objectives: Secondary

- To confirm the improvement in achievement of morphologic leukemia free state (MLS), post-induction response (CR+CRi) rate, remission duration (relapse-free survival), EFS and overall best response (CR+CRi) rate following CPX-351
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population PK of CPX-351 in patients

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- To assess and compare the pharmacoeconomic differences between CPX-351 and control

3.4 Clinical Trial Endpoints

3.4.1 Overall Survival (OS)

All randomized patients are assessed for OS. Overall survival is measured from the date of randomization to death from any cause. Patients not known to have died at last follow-up are censored on the date they were last known to be alive. Patients will be followed for a minimum of 2 years.

3.4.2 Event-free Survival (EFS)

All randomized patients are assessed for EFS. Event-free survival is defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi or death from any cause, whichever comes first. Patients alive and not known to have any of these events are censored on the date they were last examined.

3.4.3 Response Assessment Criteria

During the Treatment Phase patients will be assessed for response according to the following criteria:

Complete remission (CR) ¹	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq 1.0 \times 10^9/\text{L}$ (1000/ μL); platelet count $\geq 100 \times 10^9/\text{L}$ (100,000/ μL); independence from red cell transfusions
CR with incomplete recovery (CRi) ²	All CR criteria except for residual neutropenia ($< 1.0 \times 10^9/\text{L}$ [1000/ μL]) <u>or</u> thrombocytopenia ($< 100 \times 10^9/\text{L}$ [100,000/ μL])
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia (blasts in peripheral blood, extramedullary leukemia, or persistence in the bone marrow)
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the

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	blood, but no bone marrow examination available at recovery
Relapse ³	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

¹ Bone marrow assessment REQUIRED to confirm CR. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

² Bone marrow assessment REQUIRED to confirm CRi. Some patients may not achieve complete hematologic recovery prior to initiation of consolidation. CRi cannot be declared earlier than Day 35 to allow adequate time for documentation of peripheral blood recovery. Consolidation may begin no earlier than 42 days after the last induction course.

³ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

The response of patients with no post-baseline bone marrow assessment is entered as not done.

3.4.3.1 Timing of response assessment

In general, the patient's response to induction therapy is made on the first day when all criteria for CR or treatment failure are met. The bone marrow assessment and the peripheral counts are not required to be performed on the same day but recovery of counts (including absence of peripheral blasts) must be performed within 14 days of the bone marrow assessment. The timing of other outcomes is recorded as follows:

After one or two induction course(s), PD is declared on the day of the bone marrow showing persistent AML.

CRi is declared on or after Day 35 when the patient's bone marrow (performed between day 35-56) demonstrates absence of leukemia and the peripheral blood counts have partially recovered but appear stable (performed at least twice between day 42-56) and no further therapy is anticipated.

For patients with sufficient blood count recovery (ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$) that consolidation therapy is planned, CRi is declared on the day consolidation therapy is initiated but the peripheral counts have not met the full CR criteria. Consolidation must begin after day 35.

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3.4.3.2 Best Response

Patients who complete the induction(s) with a response of CRi may be upgraded to a CR during or after consolidation if the patient's peripheral blood counts meet the criteria for CR after declaration of a CRi. To upgrade a response to CR both peripheral blood and bone marrow assessment must be obtained within a 14 day period of each other and all criteria for CR must be met (within a 14 day period must have full recovery AND be leukemia-free).

3.4.4 Remission Duration

Only patients achieving CR or CRi are assessed for remission duration (relapse-free survival). Remission duration is measured from the date of achievement of a remission (CR/CRi) until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined.

3.4.5 Morphologic Leukemia-free State (MLS)

All randomized patients that have at least one evaluable post-randomization bone marrow assessment are assessed for MLS. Morphologic leukemia-free state is defined as bone marrow blasts <5% AND absence of Auer rods and/or extramedullary disease.

3.4.6 Stem Cell Transplant (HSCT)

The number and percentage of patients transferred for HSCT will be quantitated and compared.

3.4.7 Safety Endpoints

Safety data will be analyzed and reported for all patients in the safety population as defined in section 4.2. Safety endpoints will include hematology, coagulation, chemistries, urinalysis, vital signs, ECG, echocardiography and adverse events (AEs). AEs will be coded using the MedDRA coding dictionary. Laboratory values will be summarized both by actual result and by toxicity grade (when available).

4.0 Populations For Analysis

Figure 4-1 describes the respective patient populations being defined for the study in a flow chart format.

4.1 Intent-to-Treat (ITT) Population

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The ITT population is all patients who have been randomized to the trial. Patients are assigned to treatment arms based on what they were “randomized” to receive. This is the primary efficacy population.

4.2 Safety Population

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin), regardless of eligibility, and have at least one post-baseline safety follow-up. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

4.3 Per Protocol Population (PPP)

These patients are a subset of the ITT population. The PPP includes all patients who have met inclusion/exclusion criteria and have received at least one dose. The analysis of transfer to HSCT will be performed on this study population.

4.4 Morphologic Leukemia-free State (MLS) Population

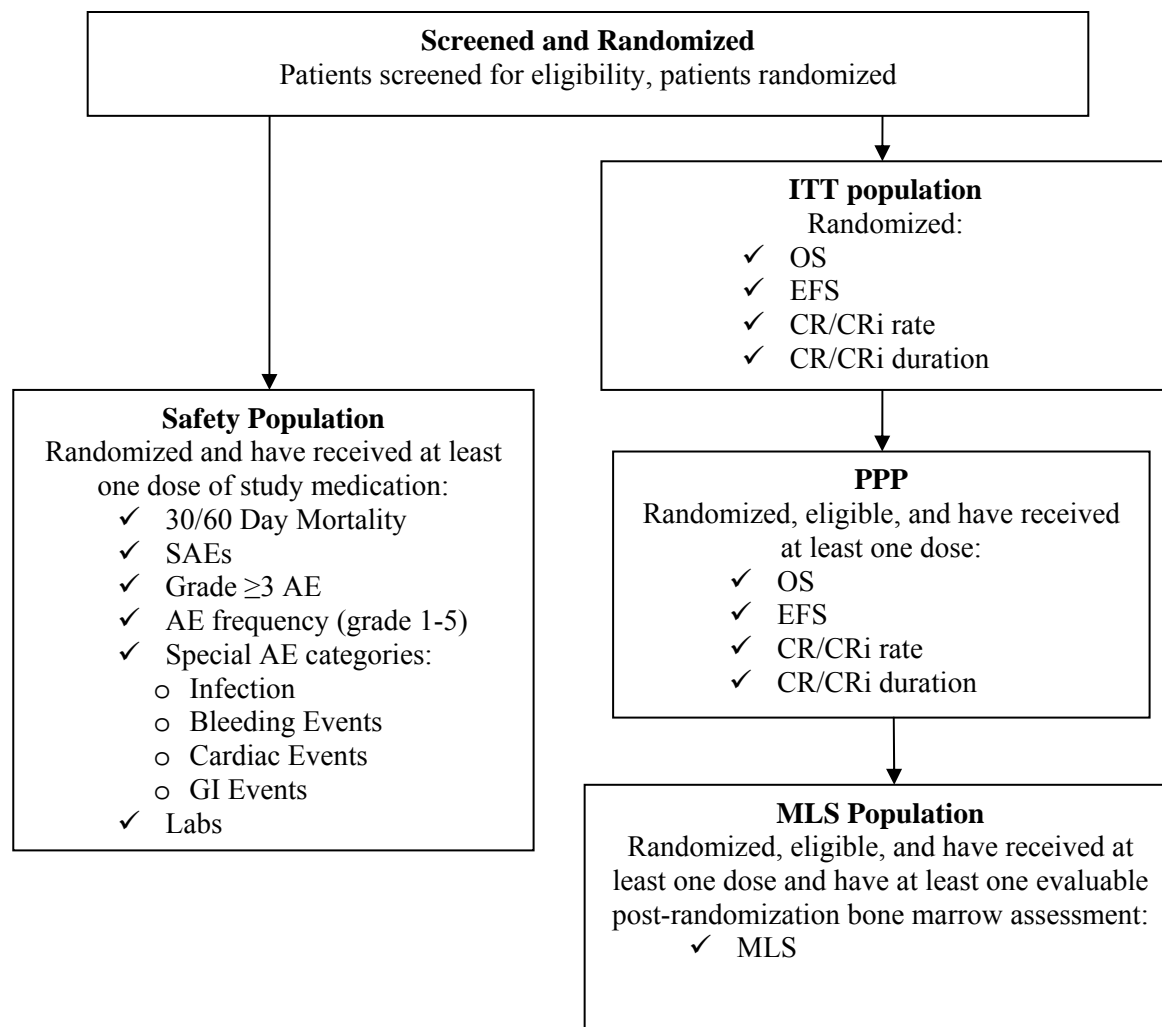
These patients are a subset of the per-protocol population. The MLS population includes all patients who have met inclusion/exclusion criteria, have received at least one dose and have at least one evaluable post-randomization bone marrow assessment performed on Day 14-21 after the last induction.

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Figure 4-1: Patient Disposition for Protocol Defined Populations



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5.0 Statistical Methods and Determination of Sample Size

5.1 Determination of Sample Size

5.1.1 Primary Efficacy Endpoint

The study will accrue 220 evaluable patients (110 per arm). An additional 20 patients (10 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on evaluable patients only and will be referred to as “patients” throughout the remainder of the statistical analysis plan. Assuming a uniform recruitment of 135 patients per year, 1.65 years will be required to complete enrollment of 220 patients. Furthermore, patients will be followed until the last patient enrolled has been followed for 1.2 years. Assuming exponential survival, and a median OS of 6 months in the control arm (Arm B), 190 deaths are expected to occur after opening of the study, resulting in a study with 94% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.6 between the two treatment arms. Total time for study completion is approximately 2.85 years.

A hazard ratio of 0.41 was observed in the 204 study for sAML patients. This study is designed to have 94% rather than 90% power for the primary endpoint to assure that the sensitivity analysis which accounts for potential early drop-outs due to transplant is adequately powered to 90% for the same hazard ratio of 0.6 and the same patient population. Please see section 5.1.3 for details on this sensitivity analysis.

5.1.2 Secondary Efficacy Endpoint

In the 204 study the observed hazard ratio for event-free survival of the 7+3 arm versus the CPX-351 arm was 1.79 (0.56) in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. This trial design with 220 patients total accrued over a period of 1.65 years with a 1.2 year follow-up yields 99% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 1.79 (0.56) between arms. This same trial design yields 90% power (with a one-sided significance level of 0.025) to detect a hazard ratio of 1.55 (0.645). These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 58% in the CPX-351 arm and 32% in the 7+3 arm. This trial design with a total of 220 patients yields 97% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 26% in

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the CPX-351 arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 32%. Based on those same assumptions, this trial design with 220 patients yield 91% power to detect a difference in responses of 23% (32% versus 55%).

5.1.3 Sensitivity Analyses

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time of transplant. This analysis will account for early drop-out due to transplant and will be performed on the ITT population. To minimize imbalances between arms due to transplant, stratification by age (see Section 3.1.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 220 patients accrued in 1.65 years, followed for 1.2 years, median OS in control group 6 months. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60. We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm still yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.60.

5.2 Data and Safety Monitoring Board (DSMB)

A data and safety monitoring board (DSMB) will be appointed and will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the clinical trial intervention during the trial, and for monitoring the overall conduct of the trial. The DSMB will periodically monitor the ongoing study for safety and efficacy considerations. The DSMB will consist of independent reviewers who are not directly involved in the conduct of the study and will advise the Sponsor of any trends or safety issues which may impact the study and/or the study patients. The DSMB will operate according to a charter. The DSMB, at a minimum, will:

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- Consist of 2 hematologists + 1 cardiologist + 1 statistician + 1 clinical operations assistant
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and at end of study to review day 60 deaths and SAEs
- Conduct a single analysis after 60 patients (30 per arm) have been evaluated for induction mortality. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB.
- A charter will be reviewed and ratified prior to the initiation of the study

5.3 Statistical Methods

5.3.1 Demographic and Baseline Comparisons

Demographics

Demographic characteristics will be summarized for all analysis populations as defined in section 4.0 (ITT population, safety population, PPP, and MLS population.) The total counts and percentages of patients will be presented for the categorical variables, both overall and by treatment arm (Table 1 in Appendix 3.) The mean, median, standard deviation, and range, will be presented for continuous variables, both overall and by treatment arm (Table 2 in Appendix 3.) Age in years (defined as the date of signed informed consent minus the date of birth divided by 365.25 days truncated to the lowest integer) will be summarized as both a continuous variable and categorical variable, with grouping done as 60-69 years and 70-75 years.

Baseline Patient Characteristics

The following patient characteristics will be collected at the Pre-Study visit and/or pre-dose: height; weight; BSA; ECOG Performance Status; vital signs; laboratory evaluations (including serum copper test); 12-lead ECG; and physical examination.

The Pre-Study visit will occur within 14 days prior to randomization. Baseline values for vital signs are defined as the last recorded values prior to first dose of study drug. For physical examination findings, baseline is defined as the last value for each body system prior to receiving the first dose of study drug.

Baseline characteristics will also be summarized for all analysis populations as defined in section 4.0 (ITT population, safety population, PPP, and MLS population.) The total counts and percentages of patients will be presented for

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the categorical variables, both overall and by treatment arm (Table 1 in Appendix 3.) The mean, median, standard deviation, and range will be presented for continuous variables, both overall and by treatment arm (Table 2 in Appendix 3.)

5.3.2 Patient Disposition

The numbers and percentages of patients who were registered (randomized) and who are included in the safety and efficacy analysis sets will be summarized, both overall and by treatment arm (Table 3 in Appendix 3.) Patients who were not registered will not be collected in the CRF, not included in the database, and not presented.

The number and percentages of patients who discontinued from the study and the reason for termination will also be presented, both overall and by treatment arm (Table 3 in Appendix 3.)

The treatment group, date of randomization, date of first dose, date of last dose, date of termination, and reason for termination will be listed for each patient who discontinues from the study (Table 4 in Appendix 3.)

5.3.3 Efficacy Analysis

5.3.3.1 Primary Endpoint Analysis

Primary efficacy analyses will be performed for the ITT population. According to the ITT principle, patients will be included in the analysis according to the randomized treatment assignment, regardless of the actual treatment received. For the primary endpoint analysis, a stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm ("7+3") (Table 5 in Appendix 3.). The test will be stratified by the stratification factors defined in section 3.1. The analysis for the primary endpoint will be performed after 190 deaths (86%) have occurred. Assuming exponential survival, uniform recruitment of 135 patients per year, an accrual period of 1.65 years, an additional follow-up period of 1.2 years and a median OS of 6 months, 190 events are expected to occur within 2.85 years after the opening of the study. The number of events is based on the alternative hypothesis.

In addition, the distribution of OS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. The Kaplan-Meier method will be used to obtain estimates for the probabilities of patients surviving. Kaplan-Meier curves will be

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presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time (Figure 1 in Appendix 3.)

A Cox proportional hazard regression analysis (Cox, 1972) will be performed to determine which prognostic factors are associated with OS. A univariate Cox regression analysis will be performed for all prognostic factors, and the resulting hazard ratios, 95% confidence intervals, and p-values will be reported (Table 6 in Appendix 3.) Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model will be run (Table 6 in Appendix 3) including a variable indicating treatment arm, allowing selection of other prognostic factors to see if the treatment effect is significant in the presence of other prognostic factors. Patients who do not have data available for all prognostic factors considered for selection in the multivariate model will be excluded from the multivariate analysis.

5.3.3.2 Secondary Endpoint Analysis

Secondary efficacy endpoints include overall post induction response (CR+CRi) rate, best response (CR+CRi) rate (after completion of the treatment phase), remission duration and EFS as defined in Section 3.4.

Secondary endpoints also include the rate of MLS and the rate of transfer for HSCT.

All efficacy analyses will be performed on an ITT basis using the ITT analysis population.

Time dependent endpoints

For the secondary time dependent endpoints (remission duration and EFS), a stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm (7+3.) (Table 5 in Appendix 3.) In addition, the distribution of these endpoints (remission duration and EFS) in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. Kaplan-Meier curves will be presented by treatment arm, with a median

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presented for each arm and a 95% confidence interval around each median time (Figure 1 in Appendix 3.)

A Cox proportional hazard regression analysis (Cox, 1972) will be performed to determine which prognostic factors are associated with these time-dependent endpoints (remission duration and EFS.) A univariate Cox regression analysis will be performed for all prognostic factors, and the resulting hazard ratios, 95% confidence intervals, and p-values will be reported (Table 6 in Appendix 3.) Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model will be run (Table 6 in Appendix 3) including a variable indicating treatment arm, allowing selection of other prognostic factors to see if the treatment effect is significant in the presence of other prognostic factors. Patients who do not have data available for all prognostic factors considered for selection in the multivariate model will be excluded from the multivariate analysis.

Binary Endpoints

The response (CR+CRi) rate and best response (CR+CRi) rate will be calculated based on the responses achieved as defined in section 3.4.3, with counts and percentages both overall and by treatment arm summarized (Table 7 in Appendix 3.) The number of patients who achieve a CR or CRi will be divided by the number of patients in the ITT analysis population.

Likewise, the rate of achieving a MLS will be calculated as the number of patients who develop this state, as defined in section 3.4.5, divided by all randomized patients who have at least one evaluable post-randomization bone marrow assessment performed on Day 14-21 after the last induction. The MLS rate will also be summarized with counts and percentages, both overall and by treatment arm (Table 7 in Appendix 3.)

The rate of transfer for SCT will be calculated by the number of patients starting conditioning treatment for SCT divided by the number of patients who have received at least one dose. This rate will also be

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summarized with counts and percentages, both overall and by treatment arm (Table 7 in Appendix 3.)

The difference in response rate, MLS rate, and rate of transfer for HSCT between the two treatment arms will be calculated using the Mantel-Haenszel test (Mantel and Haenszel, 1959). These comparisons will be stratified by the stratification factors specified in section 3.1.

A logistic regression analysis (Hosmer and Lemeshow, 2000) will also be performed to determine which prognostic factors are associated with these binary endpoints (response rate, best response rate, MLS rate, and HSCT rate.) A binary variable indicating whether a patient achieved response, best response, MLS, or HSCT will serve as the dependent variable in these analyses, respectively.

A univariate logistic regression analysis will be performed for all prognostic factors, and the resulting odds ratios, 95% confidence intervals, and p-values will be reported (Table 8a-d in Appendix 3.) Patients for whom data for a specific prognostic variable is not available will be excluded from the univariate analysis for that variable.

Additionally, exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate logistic regression model will be run (Table 8 in Appendix 3) including a variable indicating treatment arm, allowing selection of other prognostic factors to see if the treatment effect is significant in the presence of other prognostic factors. Patients who do not have data available for all prognostic factors considered for selection in the multivariate model will be excluded from the multivariate analysis.

5.3.3.3 Patient Population for Efficacy Analyses

All main analyses will be based on the ITT principle; all randomized patients are evaluable for efficacy. Patients that die on or before Day 7 will be replaced.

The primary and secondary efficacy endpoint analyses described in sections 5.3.3.1 and 5.3.3.2 above will also be repeated for the per protocol population.

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5.3.3.4 Sensitivity Analysis for Effects of Transplant on OS

A sensitivity analysis will be performed to assess the potential bias due to early drop-out due to transplant. The sensitivity analysis will be performed on the ITT population. For this analysis, patients will be censored at time of transplant. The same analyses as for the primary efficacy endpoint (section 5.3.3.1) will be performed, but with survival times censored at time of transplant for patients receiving transplant.

A stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm ("7+3"). The distribution of OS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. The Kaplan-Meier method will be used to obtain estimates for the probabilities of patients surviving. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time (Figure 1 in Appendix 3.)

A Cox proportional hazard regression analysis (Cox, 1972) will be performed to determine which prognostic factors are associated with OS. A univariate Cox regression analysis will be performed for all prognostic factors, and the resulting hazard ratios, 95% confidence intervals, and p-values will be reported (Table 6 in Appendix 3.) Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model will be run (Table 6 in Appendix 3) including a variable indicating treatment arm, allowing selection of other prognostic factors to see if the treatment effect is significant in the presence of other prognostic factors. Patients who do not have data available for all prognostic factors considered for selection in the multivariate model will be excluded from the multivariate analysis.

Results from the sensitivity analysis can then be reviewed side-by-side with the results from the primary efficacy endpoint analysis to assess the effect of early drop-out due to transplant on the results.

5.3.3.5 Sensitivity Analysis for Effects of Transplant on EFS

A sensitivity analysis will also be performed to assess the potential bias due to early drop-out due to transplant on EFS. The sensitivity analysis

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will be performed on the ITT population. For this analysis, survival times will be censored at time of transplant for patients receiving transplant. Patients who progress or relapse on or before the day of transplant will still be counted as events, but patients who have not progressed or relapsed will be censored at time of transplant. The same analyses as for the secondary efficacy EFS endpoint (section 5.3.3.2) will be performed.

A stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm (“7+3”). The distribution of EFS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time (Figure 1 in Appendix 3.)

A Cox proportional hazard regression analysis (Cox, 1972) will be performed to determine which prognostic factors are associated with EFS. A univariate Cox regression analysis will be performed for all prognostic factors, and the resulting hazard ratios, 95% confidence intervals, and p-values will be reported (Table 5 in Appendix 3.) Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model will be run (Table 5 in Appendix 3) including a variable indicating treatment arm, allowing selection of other prognostic factors to see if the treatment effect is significant in the presence of other prognostic factors. Patients who do not have data available for all prognostic factors considered for selection in the multivariate model will be excluded from the multivariate analysis.

Results from the sensitivity analysis can then be reviewed side-by-side with the results from the secondary efficacy endpoint analysis to assess the effect of early drop-out due to transplant on the results.

5.4 Details Outlining Data Quality of Formal Analysis of Primary Endpoint

5.4.1 Data Handling Rules for Primary Endpoint

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All data displays and analyses will adhere to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3, July 1996).

5.5 Safety Analyses

All patients who have received at least one dose of study medication (CPX-351, cytarabine or daunorubicin) will be considered evaluable for safety.

Safety endpoints (as defined in section 3.4.7) will be summarized. Laboratory values will be summarized both by actual result and by toxicity grade. The maximum grade for each type of toxicity will be recorded and reported for each patient, and frequency tables will be reviewed to determine toxicity patterns (Table 9 in Appendix 3.)

The laboratory data, vital signs, ECG, and echocardiography will be summarized using descriptive statistics (n, mean, standard deviation, median, range) at each scheduled time point (Table 10 in Appendix 3.) The number and proportion of patients with reported AEs will be tabulated by treatment group (Table 11 in Appendix 3.)

Early death rates (by Day 30 and 60) will be evaluated separately for each arm by the number of deaths occurring in those time intervals divided by the total number of patients in the respective arm.

All patients will have serum copper levels assessed at baseline prior to the first dose, after the last induction and at Day 150. Patients with elevated serum copper levels (>20% above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels. The proportion of patients with elevated serum copper levels after the end of treatment with CPX-351 or 7+3 will be determined for each treatment arm. Comparisons between arms will be made using the Mantel-Haenszel test (Mantel and Haenszel, 1959.) These comparisons will be stratified by the stratification factors specified in section 3.1.

5.6 Additional Endpoint Analyses

5.6.1 Pharmacokinetics

Pharmacokinetics analysis plan will be outlined in a separate document.

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5.6.2 Pharmacoeconomics

Pharmacoeconomics analysis plan will be outlined in a separate document.

5.7 Other Issues and Further Details

5.7.1 Statistical Software used in data analysis

All analyses will be performed using SAS® Version 9.2 or higher. CRAB will follow the company's SOPs in the creation and quality control of all tables, figures, listings and analyses.

5.7.2 Timing of Analyses

An analysis of induction response (CR+CRi) and 60-day death rate will be performed approximately 90-120 days after the start of treatment of the last randomized patient, which is after all patients have been accrued, treated and recovered from induction treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized, treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR+CRi) and remission duration will be performed after the endpoint for the primary analysis has occurred.

5.8 References

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6.0 Appendices

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Appendix 1: WHO Classification of Secondary Acute Myeloid Leukemia

Therapy related AML:

Requires more than 20% blood or marrow blasts AND Prior cytotoxic therapy for an unrelated disease:

- alkylating agents
- ionizing radiation therapy: large fields including active bone marrow
- topoisomerase II inhibitors
- others: antimetabolites, antitubulin agents

Acute myeloid leukemia with myelodysplasia-related changes:

Requires more than 20% blood or marrow blasts AND any of the following:

1. Previous history of myelodysplastic syndrome (MDS) requires:

Bone marrow evidence of dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryotypes	AND/OR	Unequivocal dysplasia in $< 10\%$ of cell in one or more myeloid cell lines with clonal abnormalities characteristic of MDS ¹
¹ Clonal abnormalities: Unbalanced changes: +8*, -7 or del(7q), -5 or del(5q); del(20q)*, -Y*, i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13) Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); inv(3)(q21q26.2), t(6;9)(p23;q34)		
*If the sole cytogenetic abnormality, also needs morphologic criteria with dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryotypes; all other clonal abnormalities are sufficient for a presumptive diagnosis		

OR

2. With myelodysplastic syndrome-related cytogenetic abnormalities:

- Complex karyotype (defined as 3 or more chromosomal abnormalities).
- Unbalanced: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
- Balanced: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23), t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34)

OR

3. With multilineage dysplasia

- Dysplasia present in $\geq 50\%$ of cells in at least two bone marrow cell lines
- Absence of prior cytotoxic therapy for unrelated disease AND absence of recurring cytogenetic abnormalities that meet WHO criteria for AML with recurrent genetic abnormalities.

AML with a history of CMMoL:

Requires more than 20% blood or marrow blasts AND a history of CMMoL which requires:

- Peripheral blood monocytes $> 1000/\mu\text{L}$
- Absence of Philadelphia chromosome or BCR-ABL1 fusion gene
- In the presence of eosinophilia, absence of rearrangements of PDGFRA or PDGFRB
- Presence of dysplasia in one or more myeloid lineages
- If myelodysplasia is absent/minimal the diagnosis of CMMoL may still be made if the above requirements are met and in addition there is the:
 - presence of acquired clonal cytogenetic or molecular genetic abnormality in hematopoietic cells
 - OR
 - persistence of monocytes for ≥ 3 months and
 - all other causes of monocytes have been excluded
- At diagnosis of CMMoL there are fewer than 20% blasts (myeloblast, monoblast, promonocytes) in peripheral blood and bone marrow.

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Appendix 2: Performance Status – ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

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Appendix 3: Tables and Figures

Table 1: Sample summary of demographics and baseline characteristics (categorical variables)

	CPX-351	7+3	All Patients
Factor 1	n/N (%)	n/N (%)	n/N (%)
Factor 2	n/N (%)	n/N (%)	n/N (%)
Factor 3	n/N (%)	n/N (%)	n/N (%)
Factor 4	n/N (%)	n/N (%)	n/N (%)
n/N (%): n- Number with Factor, N- Number with Valid Data for Factor			

Table 2: Sample summary of demographics and baseline characteristics (continuous variables)

	CPX-351			7+3			All Patients		
Variable	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 3	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 4	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)

Table 3: Sample summary of patient disposition (randomized population)

	CPX-351 (N=XX)	7+3 (N=XX)	All Patients (N=XX)
Patients Randomized	N	N	N
Patients (%) Safety Analysis Set	n/N (%)	n/N (%)	n/N (%)
Patients (%) Efficacy Analysis Set	n/N (%)	n/N (%)	n/N (%)
Patients (%) Efficacy Analysis Set for MLS	n/N (%)	n/N (%)	n/N (%)
Patients (%) Efficacy Analysis Set for Response	n/N (%)	n/N (%)	n/N (%)
Patients (%) with MLS During Study	n/N (%)	n/N (%)	n/N (%)
MLS after First Induction	n/N (%)	n/N (%)	n/N (%)
MLS after Second Induction	n/N (%)	n/N (%)	n/N (%)
Reason for Terminating Treatment Phase			
Adverse Event	n/N (%)	n/N (%)	n/N (%)
Consent Withdrawn	n/N (%)	n/N (%)	n/N (%)
Protocol Violation	n/N (%)	n/N (%)	n/N (%)
Lost to Follow-up	n/N (%)	n/N (%)	n/N (%)
Discretion of Investigator or Sponsor	n/N (%)	n/N (%)	n/N (%)

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	CPX-351 (N=XX)	7+3 (N=XX)	All Patients (N=XX)
Progressive Disease/Lack of Response	n/N (%)	n/N (%)	n/N (%)
Death	n/N (%)	n/N (%)	n/N (%)
Other - Transplant	n/N (%)	n/N (%)	n/N (%)
Other	n/N (%)	n/N (%)	n/N (%)
Reason for Terminating Study			
Consent Withdrawn	n/N (%)	n/N (%)	n/N (%)
Lost to Follow-up	n/N (%)	n/N (%)	n/N (%)
Death	n/N (%)	n/N (%)	n/N (%)
n/N (%): n- Number with Factor, N- Number with Valid Data for Factor			

Table 4: Sample listing of early terminations (randomized population)

Patient ID	Treatment Group	Date of Randomization	Date of First Dose (Study Day)	Date of Last Dose (Study Day)	Date Of Termination (Study Day)	Reason for Termination	If Other, Specify
01-001	CPX-351	DDMMYYYY	DDMMYYYY (XX)	DDMMYYYY (XX)	DDMMYYYY (XX)	Death Adverse Event Withdrew Consent Protocol Violation Lost to Follow-up Discretion of Investigation/Sponsor Persistent Disease /Lack of Response Other Other	XXXXXXXXX Transplant

Table 5: Sample summary of primary and secondary efficacy endpoints

Analysis	HR (95% CI)	P-value
Overall Survival (Primary Endpoint Analysis)	### (###, ###)	###
Event-Free Survival (Secondary Endpoint Analysis)	### (###, ###)	###
Remission Duration (Secondary Endpoint Analysis)	### (###, ###)	###
Overall Survival (Sensitivity Analysis)	### (###, ###)	###
Event-Free Survival (Sensitivity Analysis)	### (###, ###)	###
HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from stratified log-rank test		

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Table 6: Sample Cox regression analysis

			OS/EFS/Remission Duration	
	Variable	n/N (%)	HR (95% CI)	P-value
Univariate	Univariate Factor 1	n/N (%)	### (###, ###)	####
	Univariate Factor 2	n/N (%)	### (###, ###)	####
	Univariate Factor 3	n/N (%)	### (###, ###)	####
	Univariate Factor 4	n/N (%)	### (###, ###)	####
Multivariate	Multivariate Factor 1	n/N (%)	### (###, ###)	####
	Multivariate Factor 2	n/N (%)	### (###, ###)	####
	Multivariate Factor 3	n/N (%)	### (###, ###)	####
	Treatment Arm	n/N (%)	### (###, ###)	####
N-Number of patients with available data for specified factor, n-number of patients with specified factor HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Cox Regression				

Table 7: Sample summary of secondary efficacy binary endpoints

	CPX-351	7+3	All Patients	P-value
Post induction response (CR+CRi) rate	n/N (%)	n/N (%)	n/N (%)	####
Best response (CR+CRi) rate (after completion of treatment phase)	n/N (%)	n/N (%)	n/N (%)	####
Morphologic leukemia-free state rate	n/N (%)	n/N (%)	n/N (%)	####
Stem cell transplant rate	n/N (%)	n/N (%)	n/N (%)	####
n/N (%): n- Number with Factor, N- Number with Valid Data for Factor P-value is for comparison of rates between treatment arms and comes from the Mantel-Haenszel test.				

Table 8a: Sample logistic regression analysis for post induction response (CR+CRi) rate

		Post Induction Response (CR+CRi)				
	Variable	N (Number of patients with available data)	Achieved CR or CRi	Did Not Achieve CR or CRi	OR (95% CI)	P-value
Univariate	Univariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 4		n/N (%)	n/N (%)	### (###, ###)	####
Multivariate	Multivariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####

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		Post Induction Response (CR+CRi)				
	Variable	N (Number of patients with available data)	Achieved CR or CRi	Did Not Achieve CR or CRi	OR (95% CI)	P-value
	Multivariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Treatment Arm		n/N (%)	n/N (%)	### (###, ###)	####
N-Number of patients with available data for specified factor, n-number of patients with specified factor OR- Odds Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Logistic Regression						

Table 8b: Sample logistic regression analysis for best response (CR+CRi) rate (after completion of treatment phase)

		Best Response (CR+CRi) after completion of treatment phase				
	Variable	N (Number of patients with available data)	Achieved CR or CRi	Did Not Achieve CR or CRi	OR (95% CI)	P-value
Univariate	Univariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 4		n/N (%)	n/N (%)	### (###, ###)	####
Multivariate	Multivariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Treatment Arm		n/N (%)	n/N (%)	### (###, ###)	####
N-Number of patients with available data for specified factor, n-number of patients with specified factor OR- Odds Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Logistic Regression						

Table 8c: Sample logistic regression analysis for morphologic leukemia-free state rate

		Morphologic Leukemia-free State (MLS)				
	Variable	N (Number of patients with available data)	Achieved MLS	Did Not Achieve MLS	OR (95% CI)	P-value
Univariate	Univariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 4		n/N (%)	n/N (%)	### (###, ###)	####
Multivariate	Multivariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####

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		Morphologic Leukemia-free State (MLS)				
	Variable	N (Number of patients with available data)	Achieved MLS	Did Not Achieve MLS	OR (95% CI)	P-value
	Multivariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Treatment Arm		n/N (%)	n/N (%)	### (###, ###)	####
N-Number of patients with available data for specified factor, n-number of patients with specified factor OR- Odds Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Logistic Regression						

Table 8d: Sample logistic regression analysis for stem cell transplant rate

		Stem Cell Transplant				
	Variable	N (Number of patients with available data)	Received Stem Cell Transplant	Did Not Receive Stem Cell Transplant	OR (95% CI)	P-value
Univariate	Univariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Univariate Factor 4		n/N (%)	n/N (%)	### (###, ###)	####
Multivariate	Multivariate Factor 1		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 2		n/N (%)	n/N (%)	### (###, ###)	####
	Multivariate Factor 3		n/N (%)	n/N (%)	### (###, ###)	####
	Treatment Arm		n/N (%)	n/N (%)	### (###, ###)	####
N-Number of patients with available data for specified factor, n-number of patients with specified factor OR- Odds Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Logistic Regression						

Table 9: Sample toxicity summary

		Treatment Arm A					Treatment Arm B				
		Grade					Grade				
		1	2	3	4	5	1	2	3	4	5
System Organ Class	Preferred Term										
SOC 1	Overall	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)
	Tox Type 1	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)
	Tox Type 2	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)
	Tox Type 3	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)
SOC 2	Overall	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)	### (%)

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		Treatment Arm A					Treatment Arm B				
		Grade					Grade				
		1	2	3	4	5	1	2	3	4	5
System Organ Class	Preferred Term										
	Tox Type 1	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)
	Tox Type 2	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)	# (##%)

Table 10: Sample summary of safety data

Variable	CPX-351			7+3			All Patients		
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
PRE-STUDY									
Lab Data									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Vital Signs									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
ECG									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Echocardiography									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
DAY 14									
Lab Data									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Vital Signs									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
DAY 42									
Lab Data									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Vital Signs									
Variable 1	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)
Variable 2	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)	#	#.## (#.##)	#.## (#.##, ##.##)

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	CPX-351			7+3			All Patients		
Variable	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
Echocardiography									
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
END OF TREATMENT PHASE									
Lab Data									
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Vital Signs									
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
ECG									
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Echocardiography									
Variable 1	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)
Variable 2	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)	#	### (###)	### (###, ###)

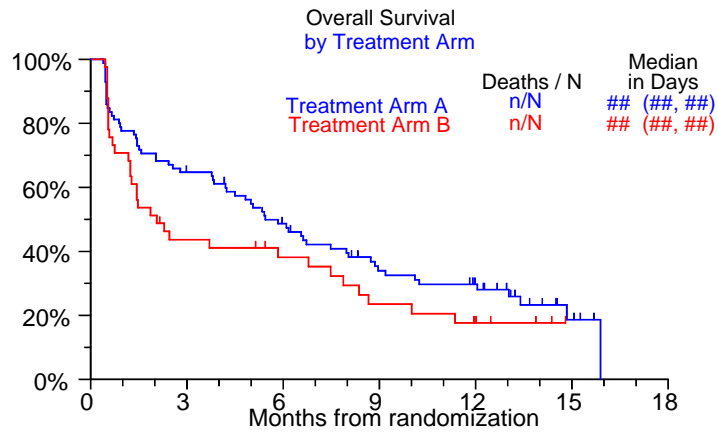
Table 11: Sample summary of adverse events

	CPX-351	7+3	All Patients
Event 1	n/N (%)	n/N (%)	n/N (%)
Event 2	n/N (%)	n/N (%)	n/N (%)
Event 3	n/N (%)	n/N (%)	n/N (%)
Event 4	n/N (%)	n/N (%)	n/N (%)
n/N (%): n- Number with Factor, N- Number with Valid Data for Factor			

Figure 1: Sample Kaplan-Meier curve

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CPX351.C.SAP.00001.V1.0

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Celator Statistical Analysis Plan

Full Title of Study	Phase III, multicenter, randomized, trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus cytarabine and daunorubicin in patients 60-75 years of age with untreated high risk (secondary) AML.
Protocol Number	CLTR0310-301
IND Reference Number	72,939
Date of Plan	February 12, 2015 Replaces: March 12, 2013
Version	3.0
Sponsor Name	Celator Pharmaceuticals, Inc.
Sponsor Address	[REDACTED]

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Revision History		
Revision	Date	Description of Change
1	March 12, 2013	Sample size increased from 240 to 300
		Added hypothesis testing for labeling purposes
		Refined definitions of study populations
		Changes to align SAP with protocol in regards to secondary endpoints
		General clarifications
2	February 12, 2015	General editorial changes for clarity
		Text added regarding exploratory analyses
		Text added indicating only select listings will be generated and these listings will be described in SAP
		Text regarding NCI CTCAE grading of labs added for clarity
		Text added to clarify patient population definitions
		Efficacy analyses by randomization stratum added
		Table numbers removed to allow for numbering changes without revising SAP
		Text regarding screen failures corrected to reflect analyses including screen failures
		Text added clarifying calculation and analysis of follow-up time
		Comparison of site versus hematopathology diagnosis added
		Text regarding response changed to reflect analyses based on hematopathology assessment
		Added analysis of transplant rate by induction response
		Added comparison of site versus hematopathology assessment of best response
		Clarified multivariate modelling

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		analyses
		Analyses for Time to Recovery endpoint added
		Data Handling rules added
		Summary and Listing of Reasons for Screen Failure added
		Added calculation of ANC when neutrophils missing

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Approvals

Printed Name	Signature	Date
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1.0 List of Abbreviations

Abbreviation	Full Term
7+3	Seven days of continuous infusion of cytarabine at 100 mg/m ² /day and three days of daunorubicin at 60 mg/m ² /day
AE	Adverse Event
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
BSA	Body Surface Area
CMMoL	Chronic Myelomonocytic Leukemia
CPX-351	CPX-351 (cytarabine: daunorubicin) Liposome Injection
CR	Complete Response
CRF	Case Report Form
CRi	Complete Response with incomplete hematologic recovery
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
HSCT	Hematopoietic Stem Cell Transplantation
ITT	Intent-to-treat
m ²	square meters
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
μL	microliter(s)
MLS	Morphologic Leukemia-free State
OS	Overall Survival
PD	Persistent Disease
PK	Pharmacokinetics

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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
t-AML	Therapy-related AML
WHO	World Health Organization

2.0 Introduction

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the study entitled: "Phase III, multicenter, randomized, trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus cytarabine and daunorubicin in patients 60-75 years of age with untreated high risk (secondary) AML."

The purpose of this document is to ensure the credibility of the study outcomes by pre-specifying the statistical approaches and data handling conventions for key analyses. This plan will focus on the analysis of the primary endpoint, which is overall survival (OS) and the secondary endpoints, which are the safety of CPX-351, morphologic leukemia free state, response (post-induction response (CR, CR+CRi), remission duration (relapse-free survival) and best post-treatment response), event-free survival (EFS), and additional CPX-351 safety measures. The primary analyses of all endpoints will be described, the populations for analysis defined, and all of the rules specified for "data handling" relevant to undertaking the key analyses. The analysis of pharmacokinetics (PK) and pharmacoeconomics will be covered in separate documents.

Some assumptions in this analysis plan are based on a prior Phase II study, Protocol CLTR0308-204 ("Study 204"), which enrolled newly diagnosed AML patients 60-75 years of age.

All analyses and data displays will adhere to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3, July 1996).

Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report as a post hoc analysis or change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created.

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3.0 Study Objectives and Endpoints

3.1 Overview of Study

This study is an open-label, randomized Phase III study, where newly diagnosed AML patients (including t-AML, AML in patients with a history of MDS or CMMoL, and de novo AML in patients with specific adverse karyotypic changes (per WHO definitions)) are randomized with equal allocation to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). Approximately 300 patients will be accrued and randomized to obtain 270 evaluable patients. Additional patients will be recruited for each patient who dies within seven days of study entry to prevent potential loss in power. Patients are stratified by age and AML subtype at randomization to balance these prognostic factors across treatment arms. This study will use a dynamic allocation procedure to allocate an equal number of patients to each of the treatment regimens. The procedure will balance the marginal distribution of the stratification factors between these treatment regimens.

3.1.1 Stratification and Randomization Scheme

At registration, patients will be randomized to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (7+3 regimen) (Study Arm B). Only patients determined to be eligible following a pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow) and confirmation of secondary AML by WHO criteria will be randomized (Appendix 1.) Patients will be stratified on the following factors:

Strata	
Age	Age 60-69 years OR Age 70-75
AML Type	<ul style="list-style-type: none">• Therapy-related AML: t-AML• MDS transformed to AML with prior HMA treatment: <u>MDS</u>AML• MDS transformed to AML without prior HMA treatment: <u>MDS</u>AML• CMMoL transformed to AML: <u>CMMoL</u>AML• De novo AML with MDS karyotype: <u>de novo</u>AML

3.1.2 Dynamic Randomization Algorithm

A dynamic balancing randomization algorithm will be used to ensure that the assignment of treatments is balanced across all the stratification factors. This procedure balances the marginal distribution of the stratification factors between these treatment regimens. The approach used is based on the method described by Pocock and Simon (Pocock and Simon, 1975).

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3.2 Study Objectives: Primary

- To confirm the efficacy of CPX-351 compared to 7+3 as first line therapy in elderly patients (60-75 years) with secondary AML. The primary efficacy endpoint will be OS.

3.3 Study Objectives: Secondary

- To confirm the safety of CPX-351
- To confirm the improvement in rate of morphologic leukemia free state, post-induction response (CR, CR+CRi) rate (morphologic, cytogenetic and molecular response), remission duration (relapse-free survival), event-free survival and overall best post-treatment response (CR, CR+CRi) rate
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To assess serum copper elevations
- To assess the population PK of CPX-351 in patients
- To assess and compare the pharmacoeconomic differences between CPX-351 and control

3.4 Clinical Trial Endpoints

3.4.1 Overall Survival (OS)

All randomized patients are assessed for OS. Overall survival is measured from the date of randomization to death from any cause. Patients not known to have died at last follow-up are censored on the date they were last known to be alive.

3.4.2 Event-free Survival (EFS)

All randomized patients are assessed for EFS. Event-free survival is defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi or death from any cause, whichever comes first. Patients alive and not known to have any of these events are censored on the date they were last examined.

3.4.3 Response Assessment Criteria

During the Treatment Phase patients will be assessed for response by the site investigator according to the following criteria:

Complete remission (CR) ¹	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq 1.0 \times 10^9/L$ (1000/ μL); platelet count $\geq 100 \times 10^9/L$ (100,000/ μL); independence from red cell transfusions
CR with	All CR criteria except for residual neutropenia ($<1.0 \times 10^9/L$)

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incomplete recovery (CRi) ²	[1000/ μ L]) <u>or</u> thrombocytopenia ($<100 \times 10^9/L$ [100,000/ μ L])
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia (blasts in peripheral blood, extramedullary leukemia, or persistence in the bone marrow)
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available at recovery
Relapse ³	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

¹ Bone marrow assessment REQUIRED to confirm CR. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

² Bone marrow assessment REQUIRED to confirm CRi. Some patients may not achieve complete hematologic recovery prior to initiation of consolidation. CRi cannot be declared earlier than Day 35 to allow adequate time for documentation of peripheral blood recovery. Consolidation may begin no earlier than 42 days after the last induction course.

³ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

The response of patients with no post-baseline bone marrow assessment is entered as not done.

Responses are confirmed by an independent hematopathology assessment indicating confirmation of CR, confirmation of CRi, Response not confirmed or Response unknown/Insufficient documentation. For response analyses, the independent hematopathology assessment will be used.

3.4.3.1 Timing of induction response assessment

In general, the patient's response to induction therapy is made on the first day when all criteria for CR or treatment failure are met. The bone marrow assessment and the peripheral counts are not required to be

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performed on the same day but recovery of counts (including absence of peripheral blasts) must be performed within 14 days of the bone marrow assessment. The timing of other outcomes is recorded as follows:

After one or two induction course(s), PD is declared on the day of the bone marrow showing persistent AML.

CRi is declared on or after Day 35 when the patient's bone marrow (performed between day 35-56) demonstrates absence of leukemia and the peripheral blood counts have partially recovered but appear stable (performed at least twice between day 35-56) and no further induction therapy is anticipated.

For patients with sufficient blood count recovery ($ANC \geq 500/\mu L$ and platelets $\geq 50,000/\mu L$) that consolidation therapy is planned, CRi is declared on the day consolidation therapy is initiated but the peripheral counts have not met the full CR criteria. Consolidation must begin after day 35.

3.4.3.2 Best Response

Patients who complete the induction(s) with a response of CRi may be upgraded to a CR during or after consolidation if the patient's peripheral blood counts meet the criteria for CR after declaration of a CRi. To upgrade a response to CR both peripheral blood and bone marrow assessment must be obtained within a 14 day period of each other and all criteria for CR must be met (within a 14 day period must have full recovery AND be leukemia-free).

3.4.4 Remission Duration

Only patients achieving CR or CRi are assessed for remission duration (relapse-free survival). Remission duration is measured from the date of achievement of a remission (CR/CRi) until the date of relapse or death from any cause; for patients whose best response is upgraded from CRi to CR, remission duration for CR+CRi analyses is calculated from the date of CRi to relapse or death. Patients not known to have relapsed or died at last follow-up are censored on the date they were last examined.

3.4.5 Morphologic Leukemia-free State (MLS)

All randomized patients that have at least one evaluable post-randomization bone marrow assessment are assessed for MLS. Morphologic leukemia-free state is defined as bone marrow blasts $< 5\%$ AND absence of Auer rods and/or extramedullary disease.

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3.4.6 Stem Cell Transplant (HSCT)

The number and percentage of patients undergoing HSCT after induction treatment will be summarized overall and by treatment group and for each category of induction response (CR, CRi or not a CR/CRi).

3.4.7 Safety Endpoints

Safety data will be analyzed and reported for all patients in the safety population as defined in section 4.2. Safety endpoints will include hematology, coagulation, chemistries, urinalysis, vital signs, ECG, echocardiography and adverse events (AEs). AEs will be coded using the MedDRA coding dictionary. Laboratory tests will be summarized by actual result and selected tests will be summarized by toxicity grade according to NCI CTCAE Version 3. Non-numeric components of the CTC grading algorithm (such as a criterion requiring hospitalization) will not be included in the calculation.

4.0 Populations For Analysis

Figure 4-1 describes the respective patient populations being defined for the study in a flow chart format. Patients who die within 7 days and are replaced will be included in study populations as long as they meet the criteria described below.

4.1 Intent-to-Treat (ITT) Population

The ITT population is all patients who have been randomized to the trial. Patients are assigned to treatment arms based on what they were “randomized” to receive. This is the primary efficacy population.

4.2 Safety Population

All patients who receive at least one dose of study medication (CPX-351, cytarabine or daunorubicin), regardless of eligibility, are in the safety population. Safety will be analyzed using the safety population. Patients are assigned to treatment arm based on what they receive.

4.3 Per Protocol Population (PPP)

These patients are a subset of the ITT population. The PPP includes all patients who meet inclusion/exclusion criteria, receive at least one dose of study medication, and have AML diagnosis and type confirmed by an independent pathologist. The analysis of transfer to HSCT will be performed on this study population.

4.4 Morphologic Leukemia-free State (MLS) Population

These patients are a subset of the per-protocol population. The MLS population includes all patients who meet inclusion/exclusion criteria, receive at least one dose of study medication, have AML diagnosis and type confirmed by an independent

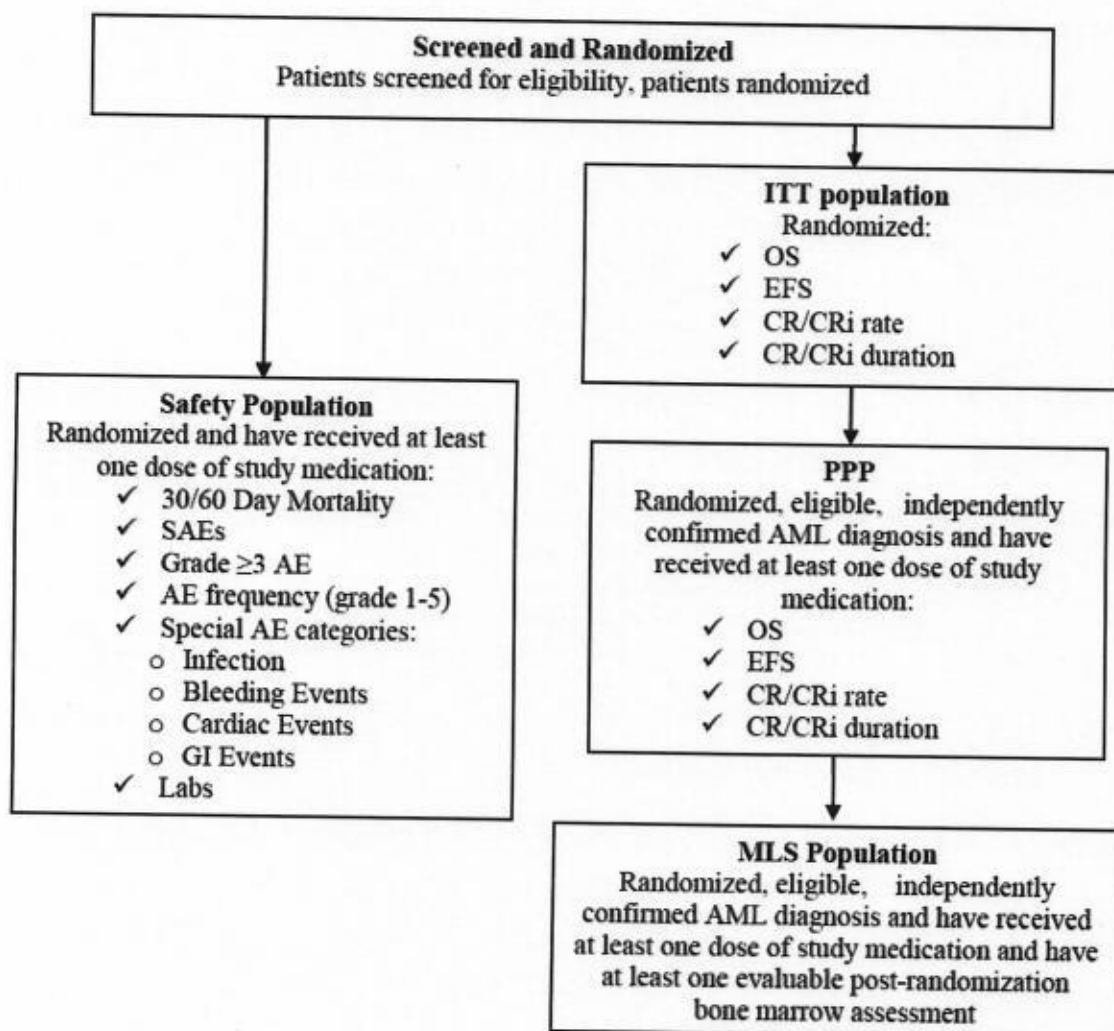
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pathologist, and have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction.

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Figure 4-1: Patient Disposition for Protocol Defined Populations



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5.0 Statistical Methods and Determination of Sample Size

5.1 Determination of Sample Size

5.1.1 Primary Efficacy Endpoint

The study will accrue 270 patients (135 per arm). An additional 30 patients (15 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. All sample size and power justifications are based on 270 patients only and these patients will be referred to as “patients” throughout the remainder of Section 5.1. The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 patients per year, an accrual period of 2 years, an additional follow-up period of 1.2 years and a median OS of 0.526 years in the control arm (Arm B), 236 deaths are expected to occur within 3.2 years after the opening of the study. This results in a study with 93.7% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 between the two treatment arms.

When the eligibility criteria of the Phase III study is applied to the sAML patients enrolled in the 204 Phase II study a hazard ratio of 0.40 is observed. This study is designed to have 93.7% rather than 90% power for the primary endpoint to assure that the sensitivity analysis which accounts for the impact of transplant on survival is adequately powered to 90% for the same hazard ratio of 0.635 and the same patient population. Please see section 5.1.3 for details on this sensitivity analysis.

5.1.2 Secondary Efficacy Endpoint

In the 204 study the observed hazard ratio for event-free survival of the CPX-351 arm versus the 7+3 arm was 0.35 in the patient population with secondary AML. The observed median event-free survival in the control arm was 42 days. The Phase III trial design with 270 patients total accrued over a period of 2 years with a 1.2 year follow-up yields >99.9% power and a one-sided significance level alpha of 0.025 to detect a hazard ratio of 0.35 between arms. These calculations are based on the assumption that the events are exponentially distributed.

In the 204 study the observed response rate (CR+CRi) in secondary AML patients was approximately 74% in the CPX-351 arm and 42% in the 7+3 arm. The Phase III trial design with a total of 270 patients yields 99.99% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 32% in the CPX-351 arm. These calculations are based on the assumption that the responses are binomially distributed and that the response rate in the control arm (7+3) is 42%.

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5.1.3 Sensitivity Analyses

In the 204 study approximately 19% of patients had HSCT. A sensitivity analysis will be performed comparing overall survival in the two arms with patients censored at the time of transplant. This analysis will account for early drop-out due to transplant and will be performed on the ITT population. To minimize imbalances between arms due to transplant, stratification by age (see Section 3.1.1) will be used.

We assume the same design considerations as for the sample size calculations for the primary endpoint: 270 patients accrued in 2 years, followed for 1.2 years, median OS in control group 0.526 years. Using these design considerations and assuming a constant drop-out rate in the first year after enrollment due to transplant with a cumulative drop-out of 20% in each arm, which corresponds to a hazard rate of the competing transplant risk of 0.223, yields a study with 90% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635. We also examined the extreme cases of maximum imbalance between arms, when all drop-outs due to transplant occur in just one treatment arm. Using the same assumptions as outlined above, but assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the CPX-351 arm and no drop-out in the 7+3 arm still yields a study with 89.9% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635. Likewise, assuming a constant drop-out rate in the first year with a cumulative drop out of 40% due to transplant in the 7+3 arm and no drop-out in the CPX-351 arm yields a study with 90.2% power (and a one-sided alpha of 0.025) to detect a hazard ratio of 0.635.

5.2 Data and Safety Monitoring Board (DSMB)

A data and safety monitoring board (DSMB) will be appointed and will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the clinical trial intervention during the trial, and for monitoring the overall conduct of the trial. The DSMB will periodically monitor the ongoing study for safety and efficacy considerations. The DSMB will consist of independent reviewers who are not directly involved in the conduct of the study and will advise the Sponsor of any trends or safety issues which may impact the study and/or the study patients. The DSMB will operate according to a charter. The DSMB, at a minimum, will:

- Consist of 2 hematologists + 1 cardiologist + 1 statistician + 1 clinical operations assistant
- Hold at least five meetings: Before the study starts, at 25%, 50%, 75% of accrued patients and at end of study to review day 60 deaths and SAEs

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- Conduct a single analysis after 75 patients (37 per arm) have been evaluated for induction mortality. Study stops if the 60 day death rate in either arm is unacceptable as determined by the DSMB in accordance with the DSMB charter.
- A charter will be reviewed and ratified prior to the initiation of the study

5.3 Statistical Methods

5.3.1 Demographic and Baseline Comparisons

Demographics

Demographic characteristics will be summarized for all analysis populations as defined in section 4.0 (ITT population, safety population, PPP, and MLS population.) The total counts and percentages of patients will be presented for the categorical variables, both overall and by treatment arm. The mean, median, standard deviation, and range, will be presented for continuous variables, both overall and by treatment arm. Age in years (defined as the date of signed informed consent minus the date of birth divided by 365.25 days truncated to the lowest integer) will be summarized as both a continuous variable and categorical variable, with grouping done as 60-69 years and 70-75 years.

Baseline Patient Characteristics

The following patient characteristics will be collected at the Pre-Study visit and/or pre-dose: height; weight; BSA; ECOG Performance Status; vital signs; laboratory evaluations (including serum copper test); 12-lead ECG; and physical examination.

The Pre-Study visit will occur within 14 days prior to randomization. Baseline values for vital signs are defined as the last recorded values prior to first dose of study drug. For physical examination findings, baseline is defined as the last value for each body system prior to receiving the first dose of study drug.

Baseline characteristics will also be summarized for all analysis populations as defined in section 4.0 (ITT population, safety population, PPP, and MLS population.) The total counts and percentages of patients will be presented for the categorical variables, both overall and by treatment arm. The mean, median, standard deviation, and range will be presented for continuous variables, both overall and by treatment arm.

An independent hematopathology review of diagnosis assesses whether the patient has documentation to support AML, and whether the patient falls into the MDS, chemotherapy, CMML, cytogenetics, other or "insufficient evidence" category. Summary comparisons of the site assessment to the independent hematopathology diagnosis assessment will be presented, along with a listing reflecting data from both sources.

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Violations of Inclusion and Exclusion Criteria will also be summarized by treatment arm.

5.3.2 Patient Disposition

The numbers and percentages of patients who were registered (randomized) and who are included in the safety and efficacy analysis sets will be summarized, both overall and by treatment arm. Frequencies of reasons for screen failure based on the Sponsor's categorization will be generated along with an associated listing for patients who fail screening.

The number and percentages of patients who discontinued from the study and the reason for termination will also be presented, both overall and by treatment arm.

The treatment group, date of randomization, date of first dose, date of last dose, date of termination, and reason for termination will be listed for each patient..

Length of follow-up time will be analyzed using Kaplan-Meier techniques, with time computed from date of randomization to last on-study date, or date of last contact. Patients who die prior to discontinuing from the study will be censored at their date of death.

5.3.3 Efficacy Analysis

All efficacy analyses will be performed on an ITT basis using the ITT analysis population unless otherwise noted. Efficacy analyses will be presented overall and for each randomization stratum; analyses by randomization stratum will not present p-values. For all treatment comparisons involving odds ratios or hazard ratios, these ratios will be computed using CPX-351 values in the numerator and the control arm values in the denominator.

5.3.3.1 Primary Endpoint Analysis

Primary efficacy analyses will be performed for the ITT population. According to the ITT principle, patients will be included in the analysis according to the randomized treatment assignment, regardless of the actual treatment received. For the primary endpoint analysis, a stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm ("7+3"). The test will be stratified by the stratification factors defined in section 3.1. The analysis for the primary endpoint will be performed after 236 deaths have occurred. Assuming exponential survival, uniform recruitment of 135 patients per year, an accrual period of 2 years, an additional follow-up period of 1.2 years and a median OS of 0.526 years, 236 events are expected to occur within 3.2 years after the opening of the study. The number of events is based on the alternative hypothesis.

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In addition, the distribution of OS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. The Kaplan-Meier method will be used to obtain estimates for the probabilities of patients surviving. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time.

A Cox proportional hazard regression analysis (Cox, 1972) stratified by age and AML type will be performed to determine which prognostic factors are associated with OS. A univariate Cox regression analysis will be performed for treatment arm and selected prognostic factors. These factors will be finalized prior to database lock and included in an addendum to this SAP. The resulting hazard ratios for each prognostic factor, associated 95% confidence intervals, and p-values will be reported. Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model, also stratified by age and AML type, will be built from prognostic factors with univariate p-values of 0.10 or less, forcing treatment in the model. Prognostic factors will be chosen for inclusion in the multivariate model using a stepwise selection algorithm, with factors kept in the model if their p-value is ≤ 0.05 . The multivariate model will assess if the treatment effect is significant in the presence of other prognostic factors.

5.3.3.2 Secondary Endpoint Analysis

Secondary efficacy endpoints include overall post induction response (CR, CR+CRi) rate, best response (CR, CR+CRi) rate (after completion of the treatment phase), remission duration and EFS as defined in Section 3.4.

Secondary endpoints also include the rate of MLS and the rate of transfer for HSCT.

Time to event endpoints

For the secondary time dependent endpoints (remission duration and EFS), a stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm (7+3.). In addition, the distribution of these endpoints (remission duration and EFS) in each arm will be estimated using the method of Kaplan-Meier (Kaplan and

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Meier, 1957) by treatment group. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time.

A Cox proportional hazard regression analysis (Cox, 1972) stratified by age and AML type will be performed to determine which prognostic factors are associated with response duration and EFS. A univariate Cox regression analysis will be performed for treatment arm and selected prognostic factors, and the resulting hazard ratios, 95% confidence intervals, and p-values will be reported. Patients for whom data for a specific prognostic factor is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate Cox regression model, also stratified by age and AML type, will be built from prognostic factors with univariate p-values of 0.10 or less, forcing treatment in the model. Prognostic factors will be chosen for inclusion in the multivariate model using a stepwise selection algorithm, with factors kept in the model if their p-value is ≤ 0.05 . The multivariate model will assess if the treatment effect is significant in the presence of other prognostic factors. The resulting multivariate model will be re-run in a non-stepwise manner to allow for inclusion of the maximum number of patients in the analysis.

Binary Endpoints

The response (CR+CRi, CR) rate and best response (CR+CRi, CR) rate will be calculated based on the responses achieved as defined in section 3.4.3 based on the independent hematopathologist's assessments, with counts and percentages both overall and by treatment arm summarized. The number of patients who achieve a CR or CRi will be divided by the number of patients in the ITT analysis population. Likewise, the number of patients who achieve a CR will be divided by the number of patients in the ITT analysis population.

Likewise, the rate of achieving a MLS will be calculated as the number of patients in the MLS population who develop this state, as defined in section 3.4.5, divided by the number of all MLS population patients who have at least one evaluable post-randomization bone marrow assessment performed on or after Day 14 after the last induction. The MLS rate will

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also be summarized with counts and percentages, both overall and by treatment arm.

The rate of HSCT will be calculated based on the number of patients receiving autologous or allogeneic transplants using the ITT population. This rate will be summarized with counts and percentages, both overall and by treatment arm.

HSCT rates will also be presented for each category of induction response (CR, CRi or < CRi).

The difference in response rate, MLS rate, and HSCT rate between the two treatment arms will be calculated using the Mantel-Haenszel test (Mantel and Haenszel, 1959). These comparisons will be stratified by the stratification factors specified in section 3.1.

A logistic regression analysis (Hosmer and Lemeshow, 2000) will also be performed to determine which prognostic factors are associated with binary efficacy endpoints (response rate, best response rate, MLS rate, and HSCT rate.) A binary variable indicating whether a patient achieved response, best response, MLS, or HSCT will serve as the dependent variable in these analyses, respectively.

A univariate logistic regression analysis will be performed for selected prognostic factors, and the resulting odds ratios, 95% confidence intervals, and p-values will be reported for each prognostic factor as well as treatment arm. Patients for whom data for a specific prognostic variable is not available will be excluded from the univariate analysis for that variable.

Exploratory multivariate analyses will be performed to assess the effect of treatment in the presence of other key prognostic factors. A multivariate logistic regression model, stratified by age and AML type, will be built from prognostic factors with univariate p-values of 0.10 or less, forcing treatment in the model. Prognostic factors will be chosen for inclusion in the multivariate model using a stepwise selection algorithm, with factors kept in the model if their p-value is ≤ 0.05 . The multivariate model will assess if the treatment effect is significant in the presence of other prognostic factors. The resulting multivariate model will be re-run in a non-stepwise manner to allow for inclusion of the maximum number of patients in the analysis.

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Hypothesis Testing for Labeling Purposes

In order to control the type 1 error at 0.025, a hierarchical testing procedure (Gatekeeping) will be implemented for testing the secondary endpoints of CR and CR+CRi. We will test the following three hypotheses:

H1: Overall Survival (OS):

- $H_0: HR_A(OS) \geq HR_B(OS)$ (there is no treatment difference in failure rates between experimental arm and control arm or the failure rate is greater in the experimental arm).
- $H_A: HR_A(OS) < HR_B(OS)$ (the failure rate in the experimental arm is lower than the failure rate in the control arm).

H2: Best Response Rate (CR):

- $H_0: CR_A \leq CR_B$ (the response rate in the experimental arm is less than or equal to the response rate in the control arm).
- $H_A: CR_A > CR_B$ (the response rate in the experimental arm is greater than the response rate in the control arm).

H3: Best Response Rate (CR+CRi):

- $H_0: (CR+CRi)_A \leq (CR+CRi)_B$ (the response rate in the experimental arm is less than or equal to the response rate in the control arm).
- $H_A: (CR+CRi)_A > (CR+CRi)_B$ (the response rate in the experimental arm is greater than the response rate in the control arm).

The three hypotheses (primary, secondary endpoint of best response (CR), and secondary endpoint of best response (CR+CRi)) will be tested in the following order:

H1: If the one-sided p-value is ≤ 0.025 for overall survival, then reject the null hypothesis and proceed to test H2. Otherwise stop all further testing and do not reject the null hypothesis for OS.

H2: If the one-sided p-value is ≤ 0.025 for best response (CR), then reject the null hypothesis and proceed to test H3. Otherwise stop all further testing and do not reject the null hypothesis of best response rate (CR).

H3: If the one-sided p-value is ≤ 0.025 , reject the null hypothesis. Otherwise do not reject the null hypothesis of best response rate (CR+CRi).

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5.3.3.3 Patient Population for Efficacy Analyses

All main analyses will be based on the ITT principle; all randomized patients are evaluable for efficacy. Patients that die on or before Day 7 will be replaced, but are included in the ITT population.

The primary and secondary efficacy endpoint analyses will also be repeated for the per protocol population.

5.3.3.4 Sensitivity Analysis for Effects of Transplant on OS

A sensitivity analysis will be performed to assess the potential bias due to transplant. The sensitivity analysis will be performed on the ITT population. For this analysis, patients will be censored at time of transplant. The same analyses as for the primary efficacy endpoint (section 5.3.3.1) will be performed, but with survival times censored at time of transplant for patients receiving transplant.

A stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm ("7+3"). The distribution of OS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. The Kaplan-Meier method will be used to obtain estimates for the probabilities of patients surviving. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time.

An additional exploratory sensitivity analysis of overall survival may be performed if there is a significant difference between the treatment arms in the proportions with HSCT (using the C-M-H test described in Section 5.3.3.2). If the HSCT rates differ significantly, a time-dependent Cox proportional regression may be performed including a time-dependent HSCT variable in the model.

Univariate and Multivariate Cox proportional hazard regression analyses (Cox, 1972) will be performed as described in Section 5.3.3.1, with the addition of censoring at the time of transplant.

Results from the sensitivity analysis can then be reviewed side-by-side with the results from the primary efficacy endpoint analysis to assess the effect of early drop-out due to transplant on the results.

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5.3.3.5 Sensitivity Analysis for Effects of Transplant on EFS

A sensitivity analysis will also be performed to assess the potential bias due to transplant on EFS. The sensitivity analysis will be performed on the ITT population. For this analysis, survival times will be censored at time of transplant for patients receiving transplant. Patients who progress or relapse on or before the day of transplant will still be counted as events, but patients who have not progressed or relapsed will be censored at time of transplant. The same analyses as for the secondary efficacy EFS endpoint (section 5.3.3.2) will be performed.

A stratified log-rank test (Mantel, 1966) will be used to compare the experimental arm (CPX-351) to the control arm ("7+3"). The distribution of EFS in each arm will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957) by treatment group. Kaplan-Meier curves will be presented by treatment arm, with a median presented for each arm and a 95% confidence interval around each median time.

Univariate and Multivariate Cox proportional hazard regression analyses (Cox, 1972) will be performed as described in Section 5.3.3.1, with the addition of censoring at the time of transplant.

Results from the sensitivity analysis can then be reviewed side-by-side with the results from the secondary efficacy endpoint analysis to assess the effect of early drop-out due to transplant on the results.

5.3.3.6 Time to Recovery Endpoint

Time to recovery of peripheral blood counts of absolute neutrophils (ANC) and platelets will be computed separately for patients with one induction and patients with two inductions using Time 0 as the date of the first dose for that induction and separately using Time 0 as the date of the first dose of the first induction; these analyses will be used to assess total duration of treatment induced cytopenias. Analyses will be presented separately for patients with one or two induction cycle(s).

For patients with CR during an induction cycle, tables will be generated indicating quartiles from separate Kaplan-Meier analyses of time to platelet value of at least 100,000/uL and time to ANC level of at least 1000 /uL. For patients with CR or CRi during an induction cycle, tables will be generated indicating quartiles from Kaplan-Meier analyses of time to a platelet value of at least 20,000/uL, time to a platelet value of at least 50,000/uL and time to an ANC value of at least 500/uL. Corresponding Kaplan-Meier graphs will be presented.

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5.4 Safety Analyses

All patients who have received at least one dose of study medication (CPX-351, cytarabine or daunorubicin) will be considered evaluable for safety.

Safety endpoints (as defined in section 3.4.7) will be summarized. Laboratory values will be summarized both by actual result and by toxicity grade. When there are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

The maximum grade for each type of laboratory toxicity will be determined for each patient, and frequency tables reflecting baseline grade (in table columns) by maximum on-study grade (in table rows) will be generated by treatment group. Additional frequency tables based on lab toxicity grades will reflect toxicity categorized as hypo- or hyper (when available) by treatment group. For these tables, baseline toxicity grade (in table columns) will range from Grade 4 hypo- to Grade 4 hyper, and maximum on-study toxicity grade (in table rows) will range from Grade 4 hypo- to Grade 4 hyper, with an additional row reflecting baseline frequencies for patients with no available on-study grade. If a patient experiences both hypo- and hyper- values of equal grade, the table will reflect the value with the greatest magnitude of change from baseline.

The laboratory data and vital signs will be summarized using descriptive statistics (n, mean, standard deviation, median, range) at each scheduled time point. Vital signs tables will include descriptive statistics at each scheduled time point, as well as change from baseline at each timepoint.

AEs will be coded using MedDRA, with some categories (e.g. cardiac, bleeding and infections) re-defined a priori by the Sponsor. Preferred terms included in each sponsor-defined category will be reflected in an addendum to the SAP.

The number and proportion of patients with reported AEs will be tabulated by treatment group, overall by maximum grade and by relationship to study drug. Similar tables for AEs resulting in death, serious AEs, AEs leading to study discontinuation, AEs leading to delay of study drug dosing, AEs of grade 3 through 5 and Anthracycline-related AEs will also be generated. Individual summaries of hemorrhage, infection, bacterial infection, viral infection and fungal infection AEs will also be presented. Summaries will be generated based on Cardiac AEs overall and for Grades 3 through 5 only.

ECG summaries will present frequency table analysis of baseline ECG value (Normal vs Abnormal) by worst post-baseline value. A similar table reflecting clinically significant ECG abnormalities will also be presented.

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Echocardiology analyses will be based on LVEF. A shift table of worst on-study LVEF by baseline LVEF will be generated for each treatment group categorizing LVEF as 50 to < 60, 60 to < 70, 70 to < 80 and 80 or above. An additional summary will present descriptive statistics by treatment group and by baseline LVEF category (<10% versus $\geq 10\%$) for maximum decrease in LVEF during the course of treatment (categorized as <50% versus $\geq 50\%$). For LVEF values reported as ranges, the lowest value of the range will be used in the analysis.

Primary causes of death will be summarized along with the relation to study drug. Early death rates (by Day 7, Days 8-30, Days 31-60) will be evaluated separately for each arm by the number of deaths occurring in those time intervals divided by the total number of patients in the respective arm. Deaths will be summarized by Study Phase as well (Treatment versus Follow-up Phase). Deaths will also be summarized by period, relation to study drug and whether the death occurred in the presence of active leukemia. A listing of death data will be provided.

All patients will have serum copper levels assessed at baseline prior to the first dose, at Day 5, Day 14, after the last induction and at Day 150. Patients with elevated serum copper levels ($>20\%$ above upper limit of normal) at Day 150 will have monthly serum copper determinations until 1 year from randomization or documentation of return of serum copper to normal levels. The proportion of patients with elevated serum copper levels after the end of treatment with CPX-351 or 7+3 will be determined for each treatment arm. Comparisons between arms will be made using the Mantel-Haenszel test (Mantel and Haenszel, 1959.) These comparisons will be stratified by the stratification factors specified in section 3.1.

5.5 Analyses Not Covered in this Document

5.5.1 Pharmacokinetics

The pharmacokinetics analysis plan will be outlined in a separate document.

5.5.2 Pharmacoeconomics

The pharmacoeconomics analysis plan will be outlined in a separate document.

5.6 Data Handling Rules

5.6.1 Imputation Rules for Primary Endpoint (OS)

If a death date is missing month or day, the following imputation method will be used to calculate overall survival:

If only the death year is known and the last date the subject was known to be

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alive is in the same year, the subject's last alive date will be used as the death date. If the last alive date occurs in a previous year, the missing month and day will be imputed as the first day and month of the year (01JAN).

If the year and month are known and the last alive date is in the same year and month as the death date then the last alive date will be used. If the last alive date is in a month prior to the death month then the death day will be imputed as the first day of the month.

5.6.2 General Imputation Rules for Partial Dates

When imputation of partial dates is required for calculation of durations, a method like the one described in Section 5.4.1.1 of this document will be utilized.

5.6.3 Conversions from Days to Years, Months or Weeks

Years = # of days / 365.25

Months = # of days / 30.4375 (i.e. 365.25/12)

Weeks = # of days / 7

Values based on the above computations will be rounded to tenths.

5.6.4 Computation of Duration

Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

5.6.5 Missing normal ranges for laboratory parameters

When either the lower limit of normal, the upper limit of normal or both are missing or are not machine readable, a standardized reference range will be used.

5.6.6 Non-Numeric Laboratory Results and Calculation of Normal Ranges

Laboratory values including symbols (“<” or “>”, for example) will not be used in summary analyses. These values will be reflected in listings of the data. When there are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

5.6.7 Missing Neutrophils

When a neutrophil value is missing, if values for segmented cells and bands are available, neutrophils will be calculated as SEGS+BANDS. If the neutrophil value is missing and either SEGS or BANDS are available, the neutrophil value will be the non-missing value of SEGS or BANDS.

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5.6.8 LVEF Reported as Range

For LVEF values reported as ranges, the lowest value of the range will be used in the analysis.

5.7 Other Issues and Further Details

5.7.1 Statistical Software used in data analysis

All analyses will be performed using SAS® Version 9.2 or higher. CRAB will follow the company's SOPs in the creation and quality control of all tables, figures, listings and analyses.

5.7.2 Timing of Analyses

An analysis of induction response (CR+CRi) will be performed after all patients have been accrued and have completed induction and consolidation treatment. This response analysis will be reviewed by the DSMB along with the final study data for 60-day mortality. The purpose of this analysis is to allow decisions to be made for initializing other clinical trials of CPX-351. The sponsor believes that use of response information will not bias the conduct of the study because all patients will have been randomized, treated and followed long enough to recover from hematopoietic effect of treatment and because the remaining data to be collected on each patients consists only of relapse and survival which are simple and objective. These analyses will not affect the conduct of the trial or the alpha of the primary endpoint. All other analyses including those for overall survival, EFS, best response (CR+CRi) and remission duration will be performed after the endpoint for the primary analysis has occurred.

5.8 Proposed Outputs

A list of proposed outputs reflecting the analyses described above is found in Appendix 3.

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6.0 References

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7.0 Appendices

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Appendix 1: WHO Classification of Secondary Acute Myeloid Leukemia

Therapy related AML:

Requires more than 20% blood or marrow blasts AND Prior cytotoxic therapy for an unrelated disease:

- alkylating agents
- ionizing radiation therapy: large fields including active bone marrow
- topoisomerase II inhibitors
- others: antimetabolites, antitubulin agents

Acute myeloid leukemia with myelodysplasia-related changes:

Requires more than 20% blood or marrow blasts AND any of the following:

1. Previous history of myelodysplastic syndrome (MDS) requires:

Bone marrow evidence of dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryocytes	AND/OR	Unequivocal dysplasia in $< 10\%$ of cell in one or more myeloid cell lines with clonal abnormalities characteristic of MDS ¹
¹ Clonal abnormalities: Unbalanced changes: +8*, -7 or del(7q), -5 or del(5q); del(20q)*, -Y*, i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13) Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); inv(3)(q21q26.2), t(6;9)(p23;q34)		
² If the sole cytogenetic abnormality, also needs morphologic criteria with dysplasia present in $\geq 10\%$ of cells in one or more myeloid lineages or $\geq 10\%$ dysplastic megakaryocytes; all other clonal abnormalities are sufficient for a presumptive diagnosis		

OR

2. With myelodysplastic syndrome-related cytogenetic abnormalities:
 - Complex karyotype (defined as 3 or more chromosomal abnormalities).
 - Unbalanced: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
 - Balanced: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34)

AML with a history of CMMoL:

Requires more than 20% blood or marrow blasts AND a history of CMMoL which requires:

- Peripheral blood monocytes $> 1000/\mu\text{L}$
- Absence of Philadelphia chromosome or BCR-ABL1 fusion gene
- In the presence of eosinophilia, absence of rearrangements of PDGFRA or PDGFRB
- Presence of dysplasia in one or more myeloid lineages
- If myelodysplasia is absent/minimal the diagnosis of CMMoL may still be made if the above requirements are met and in addition there is the:
 - presence of acquired clonal cytogenetic or molecular genetic abnormality in hematopoietic cells
 - OR
 - persistence of monocytes for ≥ 3 months and
 - all other causes of monocytes have been excluded
- At diagnosis of CMMoL there are fewer than 20% blasts (myeloblast, monoblast, promonocytes) in peripheral blood and bone marrow.

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Appendix 2: Performance Status – ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

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Appendix 3: Proposed Tables, Listings and Figures

Section 14.1 Demographic Data

Demographics and Baseline Characteristics- ITT Analysis Population
Demographics and Baseline Characteristics- Safety Analysis Population
Demographics and Baseline Characteristics- PP Analysis Population
Demographics and Baseline Characteristics- MLS Analysis Population

Baseline Disease Characteristics – ITT Analysis Population

Baseline Laboratory Values – ITT Analysis Population

Patient Status – ITT Analysis Population

Patient Disposition – ITT Analysis Population

Summary of Analysis Populations and Reasons for Exclusion – ITT Analysis Population

Summary of Inclusion Criteria – ITT Analysis Population
Summary of Exclusion Criteria – ITT Analysis Population

Length of Follow-up – ITT Analysis Population

Listing of Reasons for Screen Failure
Listing of Diagnosis: Site and Hematopathology Review Assessments
Listing of Treatment Phase Early Terminations – ITT Analysis Population
Listing of Treatment Phase Early Terminations – Safety Analysis Population

Section 14.2 Efficacy Data

Summary of Primary and Secondary Efficacy Endpoints - ITT Analysis Population
Summary of Primary and Secondary Efficacy Endpoints - PP Analysis Population

Summary of Secondary Efficacy Binary Endpoints - ITT Analysis Population
Summary of Secondary Efficacy Binary Endpoints - PP Analysis Population
Summary of Secondary Efficacy Binary Endpoint of MLS-Free State Rate - MLS Analysis Population

Summary of Hypothesis Testing for Labeling

Summary of Univariate Cox Regression Analysis for Primary Efficacy Endpoint of OS - ITT Population
Summary of Multivariate Cox Regression Analysis for Primary Efficacy Endpoint of OS - ITT Population
Summary of Univariate Cox Regression Analysis for Efficacy Endpoint of OS - PP Population
Summary of Multivariate Cox Regression Analysis for Efficacy Endpoint of OS - PP Population
Sensitivity Analysis - Summary of Univariate Cox Regression Analysis for Primary Efficacy Endpoint of OS - ITT Population
Sensitivity Analysis - Summary of Multivariate Cox Regression Analysis for Primary Efficacy Endpoint of OS - ITT Population

Summary of Univariate Cox Regression Analysis for Secondary Efficacy Endpoint of Event-Free Survival - ITT Population
Summary of Multivariate Cox Regression Analysis for Secondary Efficacy Endpoint of Event-Free Survival - ITT Population
Summary of Univariate Cox Regression Analysis for Efficacy Endpoint of Event-Free Survival - PP Population
Summary of Multivariate Cox Regression Analysis for Efficacy Endpoint of Event-Free Survival - PP Population
Sensitivity Analysis - Summary of Univariate Cox Regression Analysis for Secondary Efficacy Endpoint of Event-Free Survival - ITT Population
Sensitivity Analysis - Summary of Multivariate Cox Regression Analysis for Secondary Efficacy Endpoint of Event-Free Survival - ITT Population

Summary of Univariate Cox Regression Analysis for Secondary Efficacy Endpoint of Remission Duration - ITT Population
Summary of Multivariate Cox Regression Analysis for Secondary Efficacy Endpoint of Remission Duration - ITT Population
Summary of Univariate Cox Regression Analysis for Efficacy Endpoint of Remission Duration - PP Population
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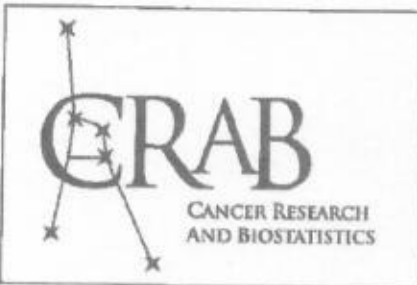
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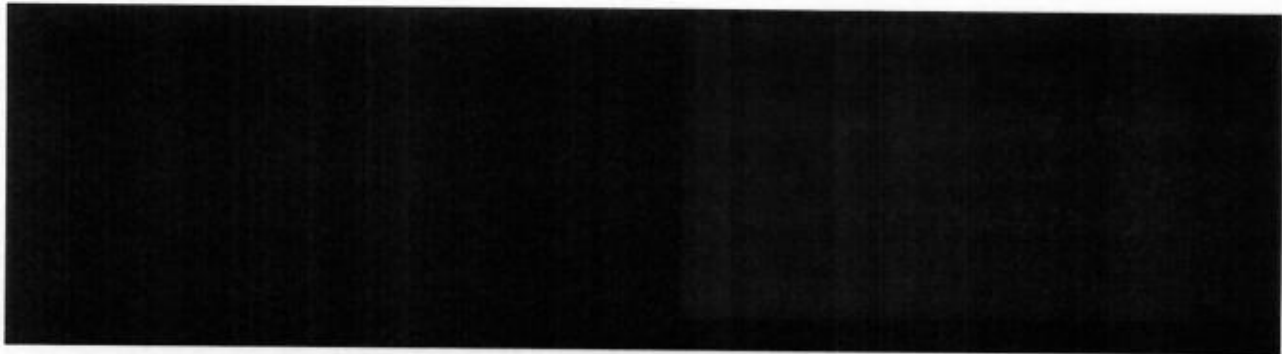


SAP Addendum

Project: PROTOCOL CLTR0310-301 PHASE III, MULTICENTER, RANDOMIZED, TRIAL OF CPX-351 (CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION VERSUS CYTARABINE AND DAUNORUBICIN IN PATIENTS 60-75 YEARS OF AGE WITH UNTREATED HIGH RISK (SECONDARY) AML.

Approval (Authorized Sponsor Representative)

By signing below, the sponsor signifies approval that the analyses provided by CRAB to the sponsor will be implemented as described in the attached SAP Addendum.



Please PDF/email to [redacted] and [redacted] (preferred)

OR

Fax the SAP addendum WITH signed signature page to CRAB Clinical Research Services at [redacted]

CLTR-0310-301 SAP Addendum

February 8, 2016

The following reflect clarifications to the planned analyses for the SAP-defined statistical analyses of CLTR-0310-301:

- (1) Study Day is calculated as (Study Date-Randomization Date)+1 if the Study Date is on or after the randomization date. Study Day is calculated as (Study Date-Randomization Date) if the Study Date is before the randomization date.
- (2) For untreated patients, baseline values will be based on the last non-missing screening value.
- (3) Only laboratory values with a numeric value and unit that are able to be converted to standard units will be included in summary tables for the given lab value.
- (4) The minimum data necessary for a complete blood count (CBC) is defined as a CBC with non-missing WBC and platelets. The minimum data necessary for a complete Serum Chemistry is defined as a serum chemistry with non-missing creatinine and bilirubin.
- (5) Prognostic variables that will be included in the univariate/multivariate models are indicated in Table A.1. Only factors with at least 15 in each category will be analyzed as indicated.
- (6) Overall survival for patients known to be alive on or after the date of the 236th event will be censored at the date of the 236th event. This also applies to other time-to-event endpoints.
- (7) For lab summaries, if there are 2 measurements on a given day, the last measurement will be used in analyses.
- (8) If patient has no death or survival status during the follow-up phase, their last contact date will be the latest of the date of their end of treatment phase and the date of non-study anti-leukemic therapy.
- (9) The MLF Population will be defined using data on or after Day 14-2 as per the protocol.
- (10) Morphologic leukemia-free state (MLF) will be measured for all subjects in the MLS population. MLF will be assessed up to the earliest of the end of follow-up or the initiation of non-study anti-leukemic therapy.

The following conditions must be met in order to classify a subject as achieving MLF:

- a) A bone marrow sample on or after day 12 shows < 5% blasts.
- b) Auer rods are not indicated as present in the bone marrow sample with < 5% blasts.
- c) If an extramedullary disease assessment was performed within +/- 14 days of the bone marrow sample showing < 5% blasts, it must be negative. Otherwise, if an assessment was not performed in this window, the last extramedullary disease assessment prior to the bone marrow sample showing < 5% blasts must be negative.

If all of these conditions are met, the subject has achieved a morphologic leukemia-free state. If unclear or missing data makes it impossible to determine the status of a subject related to a

particular bone marrow sample, it will be assumed they did not achieve a morphologic leukemia-free state at that time. If blasts are available for both the aspirate and biopsy samples, the blast percentage from the aspirate sample will be used.

- (11) In the definition of the endpoints of EFS and Remission Duration, for censoring of patients without events, the "date they were last examined" is the latest of the date of the last CBC assessment or the date of the last disease assessment. Patients will be censored on their end-of-treatment phase date if they had no disease or CBC assessments.
- (12) For univariate and multivariate modelling: If a univariate model does not converge, that prognostic variable will not be included in the multivariate model. If a multivariate model does not converge, this will be indicated in the output for that model.
- (13) ANC Values will be calculated as indicated in Table A.2. If the WBC count is below $0.5 \times 10^9/L$ then the ANC value will be imputed as $<0.5 \times 10^9/L$. All ANC values calculated with this method will be used in Time to ANC recovery analyses.
- (14) If all components of the ANC are missing and the sum of the differential components adds up to the WBC (on the absolute scale) then the ANC will be imputed as 0.
- (15) An evaluable bone marrow sample is defined as a bone marrow aspirate or biopsy determined to be adequate by the site with non-missing blasts.
- (16) For time-to-recovery analyses, patients without recovery will be censored at the date of their last hematological assessment with non-missing ANC.

Table A.1 Prognostic Factors for Multivariate Modelling

Factor	Level 1	Level 2	Level 3	Level 4
Gender	M	F		
ECOG	0	1	2	
Cytogenetic Risk*	Non-Poor	Poor		
WBC ($10^9/L$)	<20	≥ 20		
Platelet Count ($10^9/L$)	≤ 50	>50		
Hemoglobin (g/dL)	≤ 9	>9		
Bone Marrow Blast Percentage	<20%	20-40%	>40-60%	>60%
FLT3-ITD mutation	No	Yes		

*as determined by independent hematopathologist

Table A.2 ANC Calculation

Neutrophils	Segs	Bands	Granulocytes	ANC Based on:
Y	Y	Y	Y	NEUTROPHILS
Y	Y	MISSING	MISSING	NEUTROPHILS
Y	Y	Y	MISSING	NEUTROPHILS
Y	Y	MISSING	Y	NEUTROPHILS
Y	MISSING	Y	Y	NEUTROPHILS
Y	MISSING	MISSING	Y	NEUTROPHILS
Y	MISSING	Y	MISSING	NEUTROPHILS
Y	MISSING	MISSING	MISSING	NEUTROPHILS
MISSING	Y	Y	Y	SEGS + BANDS
MISSING	Y	MISSING	MISSING	SEGS
MISSING	Y	Y	MISSING	SEGS + BANDS
MISSING	Y	MISSING	Y	SEGS
MISSING	MISSING	Y	Y	GRANULOCYTES
MISSING	MISSING	MISSING	Y	GRANULOCYTES
MISSING	MISSING	Y	MISSING	NOT DONE
MISSING	MISSING	MISSING	MISSING	NOT DONE