CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209401Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 209401**
Application Type	Original 505(b)(2)
Priority or Standard	Priority
Submit Date(s)	March 31, 2017
Received Date(s)	March 31, 2017
PDUFA Goal Date	September 30, 2017
Division/Office	DHP/OHOP
Review Completion Date	August 2, 2017
Applicant	Celator Pharmaceuticals, Inc., a Jazz Pharmaceuticals company
Established Name	(Daunorubicin and Cytarabine) Liposome Injection
(Proposed) Trade Name	Vyxeos
Pharmacologic Class	Daunorubicin is an anthracycline topoisomerase inhibitor and cytarabine is a nucleoside metabolic inhibitor
Formulation(s)	Injection, lyophilized [(44 mg daunorubicin and 100 mg cytarabine) liposome]
Dosing Regimen	• Induction 1: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome days 1, 3 and 5 • Induction 2: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome days 1 and 3 • Consolidation: (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome days 1 and 3
Applicant Proposed Indication(s)/Population(s)	For the treatment of adults with (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	For the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

Note:
In some sections of this review, the dose of Vyxeos is stated in terms of units. A Vyxeos dose of (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome is equivalent to 100 units/m^2.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DGIP= Division of Gastroenterology Aand Inborn Errors Products
DHP DDS=Division of Hematology Products Deputy Director for Safety
DMEPA=Division of Medication Error Prevention and Analysis
IRT= Interdisciplinary Review Team

Glossary

AC	advisory committee
ARF	acute renal failure
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AML	Acute Myeloid Leukemia
AML-MRC	AML with myelodysplasia-related changes
BLA	biologics license application
BM	bone marrow
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Complete Remission
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HMA	Hypomethylating agent
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
t-AML	therapy-related AML
TEAE	treatment emergent adverse event
TRALI	transfusion-related acute lung injury

1 Executive Summary

1.1. Product Introduction

Trade Name:	Vyxeos®
Established Name:	(Daunorubicin and cytarabine) liposome injection
Also Known As:	CPX-351
Description:	Combination of cytarabine and daunorubicin in a 5:1 molar ratio encapsulated in liposomes. The liposome membrane is composed of distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol in a 7:2:1 molar ratio.
Dosage Forms:	Injection, lyophilized [(44 mg daunorubicin and 100 mg cytarabine) liposome]
Therapeutic Class:	Antineoplastic
Chemical Class:	Liposomal fixed small molecule combination
Pharmacologic Class:	Daunorubicin is an anthracycline topoisomerase inhibitor and cytarabine is a nucleoside metabolic inhibitor
Mechanism of Action:	After cellular internalization, the liposomes undergo degradation which releases cytarabine and daunorubicin intracellularly to induce DNA damage resulting in cell death.

Vyxeos [(daunorubicin and cytarabine) liposome injection] is a new liposomal formulation of daunorubicin and cytarabine in a fixed combination. NDA 209401 for Vyxeos was submitted for the proposed indication of "treatment of adults with (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of Vyxeos under 21 CFR 314.105 for the indication "treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)" using the following doses and schedules:

- Induction 1: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome days 1, 3 and 5
- Induction 2: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome days 1 and 3
- Consolidation: (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome days 1 and 3

The recommendation is based on the finding of a survival benefit demonstrated in Study CLTR0310-301. Further study is required to determine the incidence and nature of adverse reactions related to infusion of Vyxeos and to determine whether dose adjustments are needed for safe use in patients with renal impairment.

CLTR0310-301 (Study 301; NCT01696084) was a randomized, multicenter, open-label, active-control study which compared Vyxeos to a standard combination of daunorubicin and cytarabine (7+3) in patients 60 to 75 years old with newly-diagnosed t-AML or AML-MRC. The patients were randomized 1:1 and stratified by age and AML subtype. On the Vyxeos arm, (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome was given intravenously on days 1, 3 and 5 for the first induction and on days 1 and 3 for the second induction if needed; for consolidation, the Vyxeos dose was (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome on days 1 and 3. In the 7+3 arm, first induction consisted of daunorubicin 60 mg/m^2 on days 1, 2, and 3 and cytarabine 100 mg/m^2/day continuous infusion on days 1 through 7; second induction and consolidation cycles consisted of daunorubicin 60 mg/m^2 on days 1 and 2 and cytarabine 100 mg/m^2/day on days 1 through 5. Treatment consisted of up to 2 cycles of induction and 2 cycles of consolidation in each arm. Post remission therapy with hematopoietic stem cell transplantation (HSCT) was permitted either in place of or after consolidation.

There was no formal Vyxeos dose-ranging study that assessed efficacy in patients with newly diagnosed t-AML or AML-MRC. Dosing on days 1, 3 and 5 in induction and on days 1 and 3 in consolidation were chosen by the applicant to mimic exposure in 7+3. In a small dose-escalation trial in patients with relapsed or refractory acute leukemia or higher-risk myelodysplastic syndrome, there appeared to be a dose-response relationship, and the MTD was identified as (daunorubicin 44.4 mg/m^2 and cytarabine 101 mg/m^2) liposome. In subsequent Phase 2 studies, persistent thrombocytopenia and hemorrhage led to a dose reduction for consolidation. These results informed the dose and schedule of Vyxeos for Study 301.

Study 301 enrolled 309 patients, with 153 randomized to Vyxeos and 156 randomized to the 7+3 control arm. The randomized patients had a median age of 68 (range 60-75 years), 61% were male, and 88% had an ECOG performance status of 0 – 1. Twenty percent had t-AML, 54% had AML with an antecedent hematological disorder, and 25% had de novo AML with myelodysplasia-related cytogenetic abnormalities. The demographic and baseline disease characteristics were generally balanced between the study arms. All patients on the Vyxeos arm and 97% of those on the control arm received at least 1 cycle of induction, and 32% on the Vyxeos arm and 21% on the control arm received at least 1 cycle of consolidation. The rate of HSCT in first CR was 20% in the Vyxeos arm and 12% in the control arm.

The primary endpoint of Study 301 was OS. With an accrual target of 300 subjects and an assumed median OS of 6.3 months with standard therapy, the study had 93.7% power and a 1-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 in OS. The observed median OS in the Vyxeos arm was 9.6 months (95% CI 6.6, 11.9) compared to 5.9 months (95% CI 5, 7.8) in the control arm, with a HR of 0.69 (95% CI 0.52, 0.90) and a 2-sided stratified long-rank p-value of 0.005, indicating a survival benefit with Vyxeos treatment. In a sensitivity analysis, a trend for improved OS was maintained when OS was censored at HSCT.

Complete remission (CR) was the first alpha-controlled key secondary endpoint. All responses

considered in the analysis were as adjudicated by the FDA reviewer. CR was achieved by 38% in the Vyxeos arm and by 26% in the control arm (p=0.04). CR and CR with incomplete hematological recovery (CRi) was the next alpha-controlled secondary endpoint, but since CRi does not have established clinical benefit, the CR+CRi endpoint is not considered in this assessment of effectiveness.

Study CLTR0308-204 was a randomized Phase 2 trial comparing Vyxeos to 7+3 in patients 60-75 years of age with newly-diagnosed AML. The enrolled population included 65% with de novo AML and 35% with secondary AML. The study failed to meet its primary objective to demonstrate an improvement in CR rate. (b) (4) .

Study CLTR0308-205 was a randomized Phase 2 trial comparing Vyxeos to investigator's choice of intensive salvage therapy for patients 18 - 60 years old with AML in first relapse. The enrolled population included 90% with de novo AML and 10% with secondary AML. The study failed to meet its primary objective to demonstrate an improvement in 1-year OS. (b) (4)

It is concluded that the significant overall survival benefit and improvement in CR rate with Vyxeos in Study 301 constitutes substantial evidence of effectiveness as first line treatment of t-AML and AML-MRC. Since the biology of t-AML and AML-MRC are fairly consistent across the adult population, this efficacy outcome can be extrapolated to the full adult population.

1.3. Benefit-Risk Assessment

Table 1: Benefit-Risk Framework

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• With supportive care alone, patients with t-AML and AML-MRC survive only weeks.	t-AML and AML-MRC are fatal diseases.
Current Treatment Options	• Less than half the patients with t-AML or AML-MRC achieve remission using current available therapy, and the median survival is about 7 months.	There is a need for an effective agent for treatment of t-AML and AML-MRC.
Benefit	• In Study 301, a Phase 3 trial, 309 adults 60-75 years od were randomized to treatment with Vyxeos or 7+3 for treatment of t-AML or AML-MRC. • OS was superior in the Vyxeos arm. The HR was 0.69 (95% CI 0.52, 0.9) (p= 0.005). • The CR rate was superior in the Vyxeos arm (38% vs 26%) (p=0.036).	There is substantial evidence of effectiveness for Vyxeos as treatment for t-AML and AML-MRC.

Table 1: Benefit-Risk Framework

	Evidence and Uncertainties	Conclusions and Reasons
Risk	• In early studies, there were reactions when Vyxeos was infused over less than 90 minutes, and there are no data collected to assess for infusion reactions with slower rates of infusions. • In Study 301, the most common adverse reactions of Vyxeos were hemorrhagic events, febrile neutropenia, , rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders and vomiting. • In Study 301, patients in the Vyxeos arm had more prolonged thrombocytopenia, prolonged neutropenia, bleeding events, rash, cough, headache, visual impairment, pruritus, pneumonia, and pyrexia than on the control arm. • Each vial of Vyxeos includes 14 mg of elemental copper. • Since the APIs are identical, Vyxeos is assumed to have the same risks as other formulations of daunorubicin and cytarabine.	With the exception of the acute copper load, the safety profile of Vyxeos does not differ substantially from the current standard of care regimen, although recovery from cytopenias may be delayed more frequently. The incidence and nature of infusion reactions need to be clarified. Dosing with renal impairment needs to be determined
Risk Management	• There is potential for interchange of Vyxeos for other formulations of daunorubicin and cytarabine in the postmarket setting. • The protocol included assessments and precautions to minimize serious complications of prolonged cytopenias and anthracycline-related cardiac toxicity. • The risks of the copper load in Vyxeos are unknown and may be detrimental for patients with Wilson's disease.	Labeling should include a boxed warning regarding the difference between Vyxeos and other formulations of daunorubicin and cytarabine. It should also include warnings regarding the increased risk of hemorrhage, precautions to prevent serious cardiotoxicity, and the risks of copper overload in patients with Wilson's disease.

t-AML and AML-MRC are AML subtypes with prognosis so poor that patients with these disorders are frequently excluded of clinical trials of new therapies for AML. Study 301 provides the first evidence for benefit of a treatment for t-AML and AML-MRC, showing improved survival and remission rate with Vyxeos in comparison to 7+3. The safety profile of Vyxeos is similar to that of 7+3 with the major exception of two issues, the acute copper load and prolonged cytopenias. Both were managed on study with monitoring and precautions that can be used in labeling. Further characterization of the incidence and nature of adverse reactions related to infusion of Vyxeos and to determine whether dose adjustments are needed for safe use in patients with renal impairment can be pursued postmarketing. Although Study 301 was limited to patients $\geq$ 60 years old, the biology of t-AML and AML-MRC are fairly consistent across the adult population, so efficacy can be extrapolated to the younger patients with these disorders. And since the analyses of safety of the recommended dose showed no major issues in the adults < 60 years old, it is reasonable to conclude that the benefit-risk assessment favors approval of Vyxeos for treatment of adults with t-AML or AML-MRC.

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Acute myeloid leukemia (AML) is a heterogeneous group of hematopoietic neoplasms characterized by a clonal proliferation of myeloid precursors with limited ability to differentiate into more mature myeloid cells. These blasts replace normal hematopoietic tissue in the bone marrow, resulting in pancytopenia. According to the National Cancer Institute's SEER database, it is estimated that there will be 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017 (Siegel et al 2017). AML occurs in children and adults of all ages, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. AML is more common in men than women (5.0 vs 3.4 new cases per 100,000 persons per year) and does not have a strong racial or ethnic predilection. AML is universally fatal without treatment, with a median survival of approximately two months (Oran and Weisdorf, 2012).

Approximately 10% of patients with AML have disease that occurs after chemotherapy or radiation for an unrelated therapy, also known as therapy-related AML (t-AML). Another 20% have AML that occurs in patients with an antecedent hematologic disorder, most commonly myelodysplastic syndrome (MDS), or without an antecedent hematologic disorder, but with cytogenetic changes that are often seen with MDS. According to WHO 2016 criteria, the disease in the latter two categories are grouped together, such that AML that has evolved from MDS or a myeloproliferative neoplasm (MDS/MPN), that has established MDS-related cytogenetic abnormalities (with the exception of del(9q)), or that has dysplasia in $\geq$50% of cells in 2 or more myeloid lineages (the latter in the absence of favorable NPM1 or biallelic CEBPA mutations) are designated "AML with myelodysplasia-related changes," or AML-MRC (Arber et al 2016).

Prognosis for patients with t-AML and AML-MRC is less favorable than that for patients with de novo AML, with a median OS as low as 7-9 months reported in one Swedish registry study for patients between ages 55 and 74 (Hulegardh 2015, Leith 1997). Due to this poor survival, patients with these AML subtypes have historically been excluded from the many trials using new therapeutic agents.

2.2. Analysis of Current Treatment Options

With the exception of a rare subtype of AML called acute promyelocytic leukemia (APL), which is frequently curable with retinoic acid and arsenic trioxide and will be excluded from further discussion in this review, combination chemotherapy regimens with or without hematopoietic stem cell transplantation (HSCT) are the mainstay of therapy for patients with AML. A list of chemotherapy agents with FDA approval for the treatment of AML is provided in Table 2. In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation (the so-called "7+3" regimen) is frequently used. This regimen typically results in

CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age (Fernandez et al, 2009). However, older patients (age ≥ 60) fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20% (Estey, JCO 2006); patients with t-AML and AML with antecedent hematologic disorders have expected CR rates in the 24-51% range (Grandfeldt Ostgard et al 2015, Hulegardh 2015). While improved HSCT and supportive care regimens have reduced early death rates, only 1 new therapy has been approved (midostaurin, 2017) that confers a survival advantage in AML since the "7+3" regimen was shown to be effective in the early 1970s (Yates et al, Cancer Chemotherapy Reports 1973). There remains a clear need for new treatments for patients with AML, including those in poor-risk subgroups such as those with t-AML and AML-MRC.

Table 2: Currently Available Treatments for Acute Myeloid Leukemia

Drug	Excerpted Indication
Midostaurin	Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Cyclophosphamide	Indicated for the treatment of acute myelogenous and monocytic leukemia. Although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.
Cytarabine	Indicated, in combination with other approved anticancer drugs, for remission induction in acute non-lymphocytic leukemia of adults and children
Daunorubicin	Indicated, in combination with other approved anticancer drugs, for remission induction in acute non-lymphocytic leukemia of adults
Doxorubicin	Has been used successfully to produce regression in disseminated neoplastic conditions including acute myeloblastic leukemia
Idarubicin	Indicated, in combination with other approved anti-leukemic drugs, for the treatment of acute myeloid leukemia in adults. This includes FAB classifications M1 through M7.
Mitoxantrone	Indicated, in combination with other approved drugs, in the initial therapy of acute nonlymphocytic leukemia in adults. This category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias. Is not recommended for use during maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity. Reliance upon thioguanine alone is seldom justified for initial remission induction of acute non-lymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone
Vincristine	Indicated in acute leukemia

Source: FDA analysis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CPX-351 is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The key US presubmission regulatory activities for this submission are as follows:

- Pre-IND meeting (IND 072939) on 11/29/2005, and Study 101 initiated
- Orphan Drug Designation for CPX-351 for the treatment of patients with AML was granted on 8/22/2008
- Type C meetings for CMC/nonclinical and EOP2 meetings were held in 2010, and another EOP2 meeting was held in 2010
- A Type A clinical guidance meeting was held on 11/14/2012
- Fast Track Designation was granted for the above indication on 1/15/2015
- Breakthrough Therapy Designation was granted based on the OS results of Study 301 on 5/17/2016.
- A pre-NDA meeting was held on 5/16/2016, with an expected submission date of 8/26/2016 for the NDA. One of the issues discussed was the (b) (4) one of the facilities the sponsor used for (b) (4) A CMC meeting that included follow-up to the Agency response to this question was held on 7/13 (see below)
- A type A guidance meeting was held on 6/7/2016 to discuss the design of the label comprehension study, at which time the use of mg rather than (b) (4) for dosing was recommended by the Agency
- On 6/22/2016, in response to an Agency IR that was sent for an OSI inspection, the sponsor stated that there would be delays to the submission of the NDA, and final ADaM datasets would not be ready until 7/18/2016
- On 7/12/2013, Celator, the original sponsor, was acquired by Jazz Pharmaceuticals.
- On 7/13/2016, a Type B CMC meeting was held during which issues with internal process controls (IPC) were discussed, and the sponsor agreed to submit justification for their submission
- On 7/28/2016, the sponsor informed the agency that they had detected formatting issues with their SDTMs that could make the application potentially not fillable, and they requested rolling g submission for this NDA, with the following timeline:
    - Module 4: 9/2016
    - Module 3: 10/2016
    - Module 1, 2, 5: 12/2016 or 1/2017

  Rolling submission was granted.

- On 8/26/2016, in response to information gleaned from the OSI inspection preparation, an

IR was sent to the sponsor regarding exemptions in SAE reporting per the versions of Study 301 prior to version 2.3, how they planned to ensure identification of SAEs in the data submitted as part of the NDA, and whether this applies to the other trials in their submission; response was received on 8/31/2016 ensuring this would be included as part of the submission

- On 9/27/2016, the initial NDA presubmission was submitted (module 4)
- On 10/19/2016, there was another CMC meeting regarding the (b) (4) for one of the APIs, (b) (4) the Agency said this could not be done, but agreed to acceptance of 2 months rather than 3 of stability data at the time of submission, although this was outside of the usual protocol
- On 1/12/2017, the sponsor communicated another change in the submission schedule; Modules 5, 3, 2 and 1 would be expected on 3/30/2017
- On 2/23/2017, another CMC meeting was held with regard to specifications for the particle size, (b) (4) to ensure that the final product passes its particle size specification.
- On 3/31/2017, the NDA submission was complete

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For Study CLTR0310-301, three clinical sites (002, 004 and 031) were selected for inspection. For Study CLTR0308-205, one single clinical site (004) was selected for inspection. The classification for the inspections of clinical sites 004 and 0031 is No Action Indicated (NAI). A Form 483 was issued to the Investigator at clinical site 002 for missed laboratory tests and inaccurate reporting of laboratory test results. The classification for the inspection for clinical site 002 is Voluntary Action Indicated (VAI). Since the inaccurate test results from clinical site 002 were corrected, and the missing test results did not impact the assessment of the primary or key secondary endpoints, the study data derived from these clinical sites are considered reliable in support of the requested indication.

4.2. Product Quality

Vyxeos [(daunorubicin and cytarabine) liposome] for injection is presented as a sterile, preservative-free, purple, lyophilized cake in a 50-mL, single-dose, clear-glass vial containing 44 mg daunorubicin free base and 100 mg cytarabine free base encapsulated in liposomes. Inactive ingredients include distearoylphosphatidylcholine (DSPC) 454 mg, distearoylphosphatidylglycerol (DSPG) 132 mg, cholesterol HP 32 mg, copper gluconate 100 mg, triethanolamine 4 mg, and sucrose 2054 mg. All excipients are compendial or controlled. The container closure is a grey (b) (4) rubber stopper with aluminum flip-off cap. The drug product is supplied in cartons of 2 or 5 vials with an expiry of 48 months when stored at 2°C to 8°C (36°F to 46°F) in an upright position in the original carton protected from light.

When the drug product is reconstituted with 19 mL Sterile Water for Injection, the vial contains a purple colloidal dispersion containing daunorubicin 2.2 mg/mL and cytarabine 5 mg/mL. The reconstituted dispersion can be diluted further in 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP. The reconstituted dispersion and the diluted infusion solution are stable for up to 4 hours when stored at 2°C to 8°C.

Vyxeos drug product may contain impurities that are degradants of or related to cytarabine, daunorubicin, cholesterol, DSPC, DSPG or solvents used in manufacturing. The nonclinical reviewer concurred with the Applicant's justification to qualify the drug product impurities, and the drug product reviewer concluded that the acceptance criteria for impurities were adequate.

The drug product reviewer also identified several heavy metal impurities, but she judged the testing and final acceptance criteria to be adequate. Of note, the reconstituted drug product contains 5 mg/mL copper gluconate, of which 14% is elemental copper. In a typical patient, the maximal exposure to copper per dose of Vyxeos is 24 mg, while the maximal theoretical total

exposure of copper under the proposed Vyxeos dosing regimen is (b) (4) The permitted daily exposure (PDE) of copper is 340 µg[1] when administered parenterally. According to the label for Cupric Chloride Injection (NDA 018960), overdose of parenterally-administered copper can result in hemolysis, liver toxicity, prostration, behavior change, diarrhea, progressive marasmus, hypotonia, photophobia, and peripheral edema. No copper-related toxicity was observed in animals given CPX-351 (Section 5.5.1); however, full toxicity assessments were limited by the poor clinical condition of most animals in those studies. The clinical reviewer concluded that due to the level of this impurity, a warning was needed in labeling specifically for patients with Wilson's disease (Sections 7.4.4 and 7.4.5).

Different formulations were used in the clinical trials that form the basis of the NDA. Early phase trials used a frozen liquid formulation. The Phase 3 pivotal study, CLTR01301-301, used a lyophilized formulation which the biopharmaceutics reviewer found was not significantly different from the to-be-marketed formulation. The clinical pharmacology reviewer found no clinically meaningful difference in exposure following administration of the liquid or lyophilized formulations (Section 13.4.3), and the biopharmaceutics reviewer noted that the in vitro drug release characteristics of the different formulations were similar, so it was concluded that the clinical safety and efficacy data in the NDA are applicable to the to-be-marketed drug product.

This NDA was submitted as a 505(b)(2) application. Review required relying on the published literature and the FDA's prior findings of clinical pharmacology (i.e., metabolism and excretion pathways and drug-drug interactions with cardiotoxic agents and hepatotoxic agents) and nonclinical pharmacology/toxicology (i.e., mechanisms of action, genotoxicity, carcinogenicity, reproductive, and developmental toxicity) for the liposomal and nonliposomal daunorubicin and cytarabine listed products. The biopharmaceutics reviewer noted that the proposed liposomal product and the listed drugs contain the same active pharmaceutical ingredients (cytarabine and daunorubicin), so the Applicant's reliance on FDA's previous findings is justified for the select information. In addition, the findings of the animal pharmacology, PK, and single- and repeat dose toxicity studies were corroborative.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31. Approval of the NDA was recommended by the Product Quality review team.

4.3. Devices and Companion Diagnostic Issues

There are no companion diagnostic devices required for the proposed use of Vyxeos

[1] FDA Guidance for Industry, 2015, Q3D Elemental Impurities

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Vyxeos® (daunorubicin and cytarabine) liposome for injection (CPX-351) is a liposomal formulation of a fixed molar ratio (1:5) combination of the antineoplastic drugs daunorubicin (DN) and cytarabine (Cyt) [see Product Quality]. NDA 209401 included nonclinical data evaluating the pharmacology, pharmacokinetics (PK), and single- and repeat-dose toxicity of CPX-351. This NDA also relies on the labels of the listed drugs DepoCyt® (cytarabine liposome injection) and DaunoXome® (daunorubicin citrate liposome injection).

The Applicant demonstrated the 5:1 fixed molar ratio of Cyt:DN resulted in synergistic in vitro cytotoxicity in the majority (8/15, 53%) of cancer cell lines evaluated. The exact mechanism(s) contributing to the synergy are unknown. The in vivo antitumor activity of CPX-351 and related products were evaluated in various syngeneic and xenograft murine models. CPX-351 demonstrated greater antitumor activity than other liposomal fixed molar ratio combinations of Cyt and DN, confirming 5:1 as the optimal fixed molar ratio. CPX-351 also demonstrated greater antitumor activity than individual liposomal formulations of Cyt or DN, and non-liposomal Cyt and DN free-drug cocktail, even when the dose levels of Cyt and/or DN were greater in the comparator treatment arms.

The PK and tissue distribution of CPX-351 was evaluated in a series of pharmacology and/or PK studies in mice and rats. The comparative PK and plasma-versus-bone marrow distribution of CPX-351 and non-liposomal Cyt and DN free-drug cocktail were evaluated in non-tumor bearing mice. Following a single intravenous (IV) administration, CPX-351 was associated with increased and more sustained exposure of Cyt and DN in the plasma and bone marrow relative to the free-drug cocktail, on a dose-normalized basis. CPX-351 was stable in the plasma with >99% of Cyt and DN remaining liposome-encapsulated. In a mouse model of disseminated leukemia, CPX-351 or free-drug cocktail was administered to mice by the IV route three times 3 days apart. CPX-351 delivered higher amounts of Cyt and DN to the bone marrow than the free-drug cocktail, and both Cyt and DN accumulated in the bone marrow following repeated administrations of CPX-351. The molar ratio of Cyt:DN in the bone marrow was maintained from 5:1 to 2:1 during the 24 hours after each injection of CPX-351. The increased levels and retention of Cyt and DN in the bone marrow of CPX-351-treated mice correlated with greater eradication of leukemic bone marrow cells and prolonged survival. In a separate experiment using the same mouse model, mice were administered a single IV dose of CPX-351; 18 hours later, leukemic bone marrow cells contained 9- and 2-times more Cyt and DN than normal bone marrow cells, respectively. Together, the PK and bone marrow distribution studies indicate CPX-351 is distributed to the bone marrow; after entering bone marrow cells, the intracellular concentrations of Cyt and DN are transiently maintained near the optimal 5:1 ratio. Retention

in the bone marrow increased exposure (as measured by the area under the concentration time curve (AUC)) to both drugs and correlated with improved in vivo antitumor activity.

The comparative tissue distribution of Cyt and DN, when administered as either CPX-351 or non-liposomal Cyt or DN, was evaluated in a pair of whole body autoradiography studies in rats. Non-liposomal Cyt or DN rapidly distributed from the plasma into the tissues, with the greatest distribution to the urinary bladder wall, spleen, pituitary, pancreas, adrenal, kidney, and/or thymus. When administered as CPX-351, Cyt and DN tended to remain in the vasculature and had similar tissue distribution patterns; distribution of Cyt and DN to the bone marrow was eclipsed only by the urinary bladder wall, spleen, and/or adrenal. High distribution to the spleen is consistent with the established role of the mononuclear phagocyte system (MPS) in clearing liposomes from the circulation[2].

The Applicant conducted single- and repeat-dose toxicity studies of CPX-351 in rats and dogs; these studies were conducted using the IV route, consistent with the intended clinical route of administration. In the 2-cycle rat study, CPX-351 was administered IV at doses of 5, 10, or 15 mg/kg Q2D x 3 in a 3 week cycle, followed by a 28-day recovery period. CPX-351 was associated with morbidity at the ≥10 mg/kg dose levels such that dose-response relationships could not be determined for most parameters. Drug-related decrease in white blood cell (WBC) differential was observed that correlated with hypocellularity of the bone marrow and lymphoid organs, and reduction in thymic and spleen weight and size. Epithelial necrosis of the large and small intestinal mucosa was also observed. The reversibility of these findings could not be evaluated due to premature deaths and early terminations, which were attributed to bone marrow and lymphoid toxicity. Similarly, definitive neurologic assessments could not be conducted due to the poor clinical condition and small number of surviving animals.

In the 2-cycle dog study, CPX-351 was administered IV at doses of 1, 2, or 3 mg/kg Q2D x 3 in a 3 week cycle, followed by a 28-day recovery period. CPX-351 was associated with morbidity at the ≥2 mg/kg dose levels; morbidity was attributed to hypocellularity of the bone marrow and lymphoid organs and epithelial necrosis of the large and small intestinal mucosa. Bone marrow and lymphoid hypocellularity correlated with decrease in WBC differential. There were no electrocardiography (ECG) findings. Recovery data did not identify any hematology or histopathological changes suggesting partial or complete reversibility; however, it should be noted recovery data was limited to a small number of animals.

The primary CPX-351 target organs identified by the repeat-dose toxicity studies in rats and dogs were the bone marrow, lymphoid organs, and small and large intestines. Findings were reversible in dogs; reversibility in rats could not be evaluated due to premature deaths and early terminations. Single-dose toxicity studies were reviewed but did not identify any new

[2] Allen T, C Hansen, and D Lopes de Menezes, 1995, Pharmacokinetics of long-circulating liposomes, Adv Drug Del Rev, 16:267–284.

target organ toxicities. Taken together, the CPX-351 toxicity profile is consistent with the known toxicological effects of Cyt and DN.

No genotoxicity, carcinogenicity, or reproductive and developmental toxicity studies were conducted with CPX-351. To inform the risks of CPX-351, the Applicant references the known genotoxicity, carcinogenicity, and reproductive and developmental toxicity effects of the reference drugs DepoCyt® and DaunoXome®. According to the labels for DepoCyt® and DaunoXome®, in reproductive and developmental toxicity studies Cyt was teratogenic in mice and rats, and embryotoxic in mice, while DN was embryotoxic in rats. Both Cyt and DN were mutagenic in vitro and clastogenic in vitro and in vivo. Cyt caused the transformation of hamster and rat cells in vitro. These data support the inclusion of a warning for embryo-fetal toxicity and male and female contraception recommendations in the Vyxeos® label. The Vyxeos® label recommends effective contraception use for females and males of reproductive potential during treatment with Vyxeos® and for 6 months following the last dose, which is acceptable.

Cyt was clastogenic to meiotic cells and caused an increase in sperm-head abnormalities in mice, while DN impaired the fertility in male dogs. These data support the inclusion of a statement in the label that male fertility may be compromised by Vyxeos®.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of Vyxeos® for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In vitro studies

Five fixed molar drug ratios of Cyt:DN were evaluated in 15 cell lines for potential ratio-dependent synergy. The cell lines evaluated and their tissues of origin are in Table 3. Cells were cultured under standard laboratory conditions and treated with either free drug (Cyt or DN) or fixed molar drug ratios of Cyt:DN for 72 hours. Cell viability was then inferred with the colorimetric MTT assay. All assays were performed in triplicate, averaged, and repeated a minimum of four times. Synergy was evaluated by the median-effect principle described by Chou and Talalay[3] using the Combination Index (CI) where a CI=1.0 was considered additive, a CI>1.0 indicated antagonism, and a CI<1.0 indicated synergy.

[3] Chou, T and P Talalay, 1984, Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors, Adv Enzyme Regul, 22:27-55.

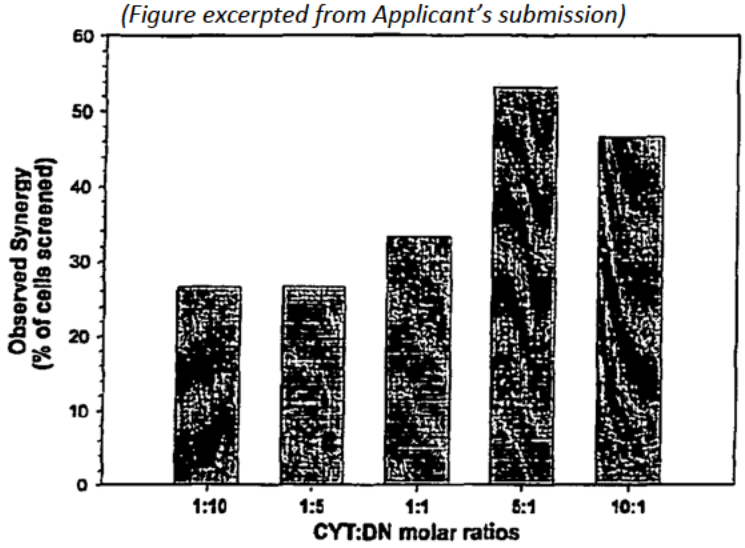
Table 3: Cancer cell lines evaluated for Cyt and DN synergy

Cell line	Tissue type	Cell line	Tissue type
A253	Head and neck	KBM-3	Leukemia
BxPc-3	Pancreatic	L1210	Leukemia
CCRF-CEM	Leukemia	LS180	Colon
Colon 26	Colon	MOLT-4	Leukemia
HCT-116	Colon	P388	Leukemia
HL60	Leukemia	SW620	Colon
HT-29	Colon	WEHI-3B	Leukemia
IGROV-1	Ovarian		

Inhibitory concentration values observed for free Cyt, free DN, and the five fixed molar drug ratios of Cyt:DN all ranged widely in the different cell lines evaluated (data not shown). The observed frequency of synergy for each molar drug ratio of Cyt:DN is in Figure 1. At the 5:1 molar drug ratio of Cyt:DN synergism was observed in 8/15 (53%) of the cell lines whereas synergism was observed in only 4/15 (27%) of the cell lines at the 1:10 and 1:5 molar drug ratios. These in vitro results indicate the optimal synergistic molar drug ratio of Cyt:DN is 5:1 in the cell lines evaluated.

Figure 1: The percentage of total cell lines screened exhibiting synergy at the indicated fixed molar ratios of Cyt:DN

(Figure excerpted from Applicant's submission)



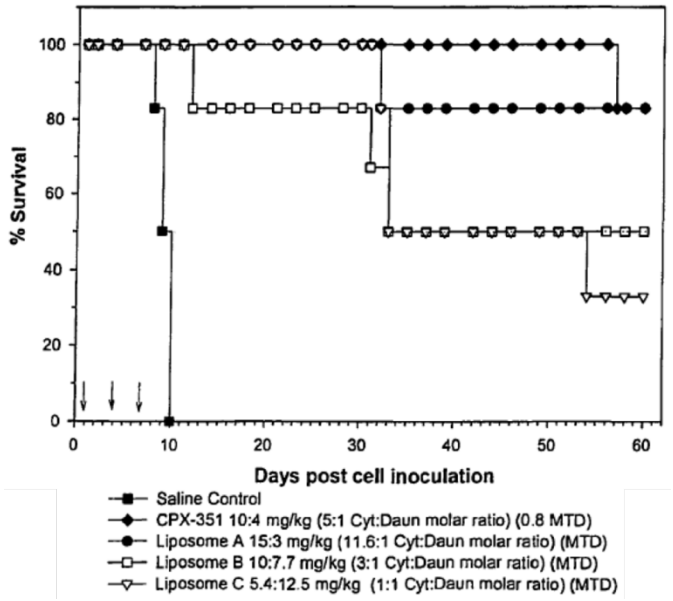
B. In vivo studies

The in vivo antitumor activities of four liposomal Cyt:DN formulations were compared using a syngeneic murine leukemia model with implanted P388 cells. Test articles were administered by the IV route on Days 1, 4, and 7 after tumor cell implantation. Antitumor activity was assessed by evaluating survival rates over time. Survival was longer in mice treated at liposomal

Cyt:DN molar ratios ≥5:1 (see Figure 2). Comparable antitumor activity was observed at the 11.6:1 and 5:1 molar ratios, however the MTD was administered at the 11.6:1 molar ratio while only 0.8-times the MTD was administered at the 5:1 molar ratio.

Figure 2: Antitumor activities of four fixed molar ratios of liposomal Cyt:DN

(Figure excerpted from Applicant's submission)



The in vivo antitumor activities of CPX-351, individual liposomal formulations of Cyt or DN, and non-liposomal Cyt and DN free-drug cocktail were compared in a series of studies conducted in syngeneic murine and human xenograft leukemia models. The antitumor activity was inferred by evaluating survival rates over time. Tolerability was evaluated by monitoring morbidity and individual mouse body weights. CPX-351 was administered at doses up to the MTD, while free and liposomal Cyt and DN were administered at ratio-matched (dose equivalents to the amount of respective agent in CPX-351) and dose pushed (based on the relative MTDs of the two drugs administered individually) dose levels. Test articles were administered by the IV route three times 3 days apart, however the exact days of administration varied by mouse model.

The antitumor activities of the test articles varied by dose level and mouse model (data not shown). CPX-351 demonstrated dose-dependent antitumor activity, with a >8-fold maximum increase in life span relative to saline control. The non-liposomal free-drug cocktail also demonstrated dose-dependent antitumor activity, however the maximum effect was smaller with only a 2-fold increase in life span relative to saline control; at higher doses the non-liposomal free-drug cocktail was not well-tolerated. Individual liposomal formulations of Cyt or DN each demonstrated dose-dependent antitumor activity; however, neither agent exhibited antitumor activity comparable to CPX-351. At their respective MTDs, liposomal Cyt and DN demonstrated a 5-fold and 3-fold increase in life span relative to saline control, respectively. In conclusion, the in vivo results demonstrate that a fixed 5:1 molar ratio of liposomal Cyt:DN (CPX-351) are optimal for overall antitumor activity, and the antitumor activity of CPX-351 was

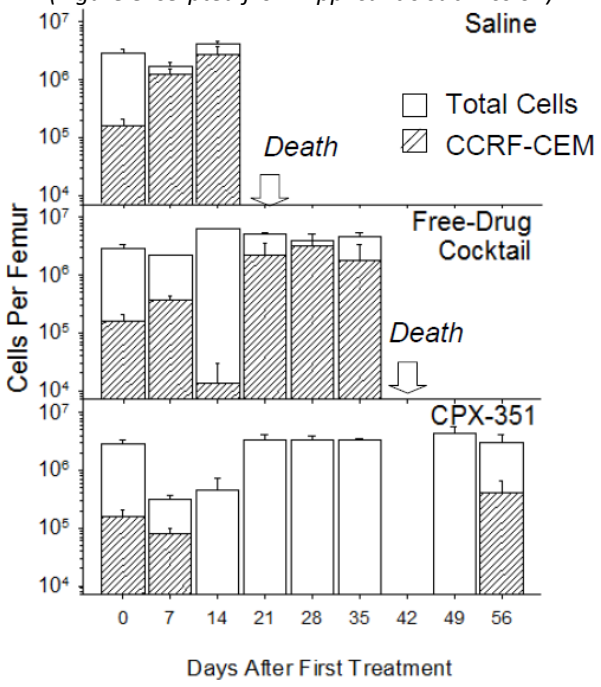
greater than the combined activity of Cyt and DN in a non-liposomal formulation or the individual activities of liposomal formulations of Cyt or DN.

The relative delivery and uptake of CPX-351 and non-liposomal Cyt and DN free-drug cocktail was evaluated with the CCRF-CEM leukemia model in Rag2-M mice. CCRF-CEM cells were injected IV; following engraftment to the bone marrow, mice were administered test articles by the IV route three times 3 days apart (dose levels of 10:4.4 mg/kg and 300:4.5 mg/kg [Cyt:DN] for CPX-351 and free-drug cocktail, respectively). Mice were sacrificed at specified time points and bone marrow cell suspensions were prepared from femurs; bone marrow cell suspensions were examined by flow cytometry. Bone marrow concentrations of Cyt and DN were determined by HPLC analysis.

CPX-351 caused reduction in total bone marrow and leukemic cells by Day 7 and abrogation of leukemic cells by Day 14 (see Figure 3); regrowth of leukemic cells was observed on Day 56. Free drug cocktail caused an initial decline in leukemic cells, however leukemic cells repopulated by Day 21, and mice died by Day 42. Leukemic cells expanded in saline-treated mice which died by Day 21.

Figure 3: Treatment effects on total bone marrow and leukemic cells

(Figure excerpted from Applicant's submission)

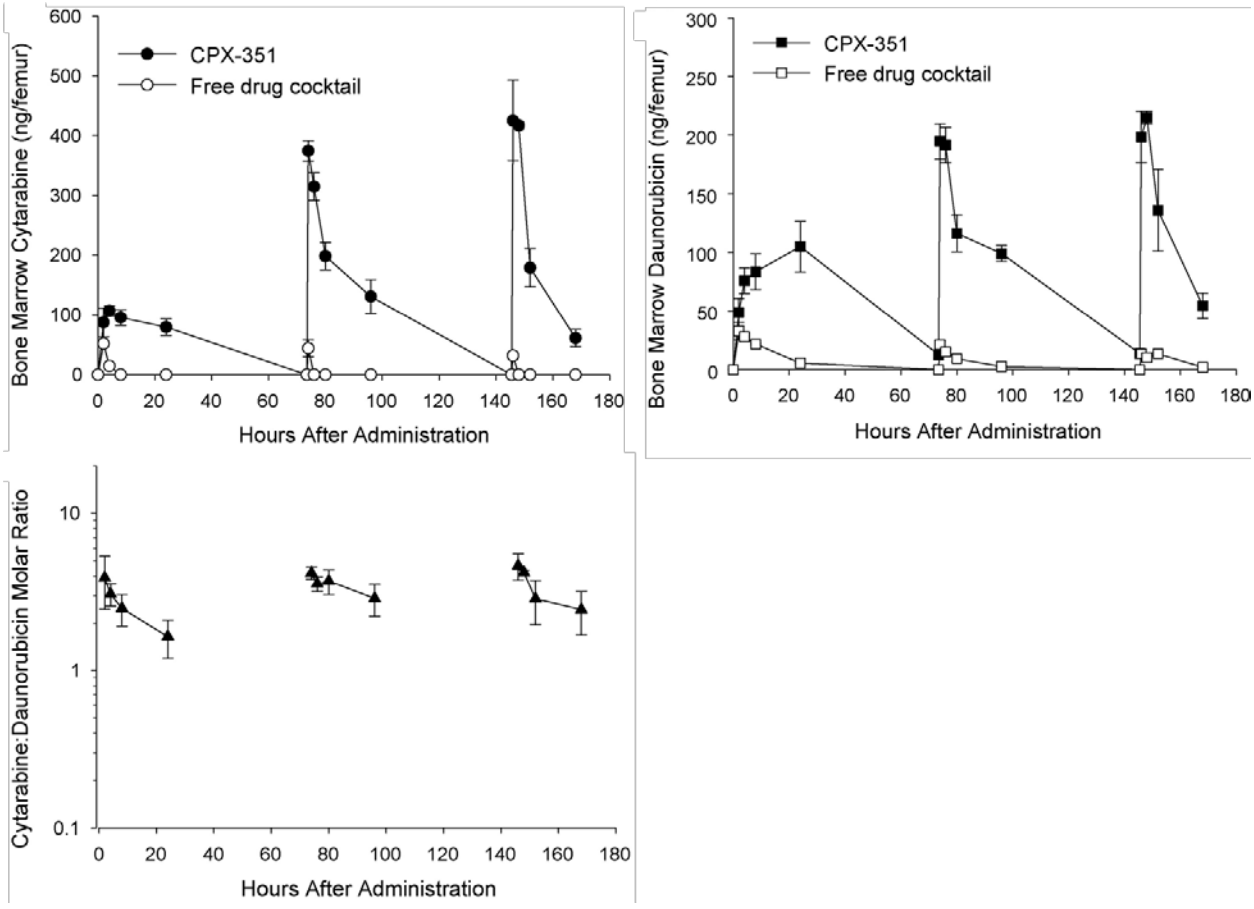


After the first CPX-351 injection, peak bone marrow levels of Cyt were 2-fold higher than that observed for the free-drug cocktail (see Figure 4, top left); after the second and third injections of CPX-351, peak Cyt levels were 7.6- and 12-fold higher, respectively. Peak bone marrow levels of DN were 3.2-, 8.8- and 14-fold higher in CPX-351 treated mice after the first, second, and third doses, respectively (see Figure 4, top right). The bone marrow exposure (as measured by

AUC) of Cyt and DN after CPX-351 treatment (relative to free-drug cocktail) was elevated by 28-, 91-, and 69-fold for Cyt, and 9-, 22-, and 14-fold for DN, after the first, second, and third injections, respectively. The molar ratio of Cyt:DN in the bone marrow was maintained from 5:1 to 2:1 during the 24 hours after each injection of CPX-351 (see Figure 4, bottom left).

Figure 4: Drug accumulation in CCRF-CEM engrafted bone marrow

(Figure excerpted from Applicant's submission)



The comparative uptake of CPX-351 into leukemia versus normal bone marrow cells was evaluated in a separate experiment in CCRF-CEM-bearing Rag2-M mice. Mice were administered a single IV injection of CPX-351; 18 hours later CCRF-CEM cells contained 9- and 2-times the Cyt and DN than normal bone marrow cells, respectively (data not shown).

Safety Pharmacology

No standalone safety pharmacology studies were conducted with CPX-351, consistent with regulatory guidance[4]. CNS and CV safety pharmacology endpoints were incorporated into the

[4] FDA Guidance for Industry, 2010, S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

rat and dog repeat-dose toxicology studies, respectively. There was no evidence of CNS or CV effects, however moribundity and mortality at the mid and high dose levels prevented a comprehensive evaluation.

The Applicant references the known effects of the listed drugs DepoCyt® and DaunoXome®. According to the label for DepoCyt®, Cyt is associated with the development of chemical arachnoiditis. According to the label for DaunoXome®, DN is associated with cardiac toxicity and congestive heart failure.

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Tissue Distribution of [^{14}C]CPX-351 and Free [^{14}C]Cytarabine-Derived Radioactivity Following a Single Intravenous Dose of [^{14}C]CPX-351 and Free [^{14}C]Cytarabine in Male Long-Evans Rats Using Quantitative Whole Body Autoradiography / Study Report (b)(4)14628

and

Tissue Distribution of [^{14}C]CPX-351, Free [^{14}C]Daunorubicin, and Free [^{3}H]Cytarabine-Derived Radioactivity Following a Single Intravenous Dose of [^{14}C]CPX-351, Free [^{14}C]Daunorubicin, and Free [^{3}H]Cytarabine in Male Long-Evans Rats Using Quantitative Whole Body Autoradiography / Study Report (b)(4)13687</td><td>Male Long-Evans rats received IV injections of ^{14}C-labeled CPX-351 or Cyt and DN as the non-liposomal formulations. Blood, plasma, and carcasses were collected at specified times up to 504 hours postdose. The tissue distribution of radioactivity was determined using quantitative whole body autoradiography.

Tissue:plasma AUC_{last} ratios for ^{14}C-Cyt and ^{14}C-DN in rats
<table>
<tr><th rowspan="2">Tissue</th><th colspan="2">CPX-351</th><th colspan="2">Non-liposomal</th></tr>
<tr><th>Cyt</th><th>DN</th><th>Cyt</th><th>DN</th></tr>
<tr><td>Plasma</td><td>1.00</td><td>1.00</td><td>1.00</td><td>1.00</td></tr>
<tr><td>Spleen</td><td>0.44</td><td>3.28</td><td>1.50</td><td>131.46</td></tr>
<tr><td>Adrenal cortex</td><td>0.24</td><td>0.57</td><td>1.15</td><td>90.87</td></tr>
<tr><td>Adrenal gland</td><td>0.26</td><td>0.64</td><td>1.13</td><td>91.87</td></tr>
<tr><td>Adrenal medulla</td><td>0.39</td><td>1.06</td><td>1.17</td><td>102.54</td></tr>
<tr><td>Urinary bladder wall</td><td>0.29</td><td>0.07</td><td>1054.5</td><td>17.62</td></tr>
<tr><td>Bone marrow</td><td>0.21</td><td>0.97</td><td>1.39</td><td>66.08</td></tr>
<tr><td>Lung</td><td>0.21</td><td>0.35</td><td>1.15</td><td>36.65</td></tr>
<tr><td>Kidney</td><td>0.15</td><td>0.39</td><td>2.81</td><td>49.61</td></tr>
<tr><td>Kidney cortex</td><td>0.14</td><td>0.37</td><td>2.15</td><td>45.55</td></tr>
<tr><td>Kidney medulla</td><td>0.16</td><td>0.42</td><td>4.23</td><td>57.41</td></tr>
<tr><td>Heart</td><td>0.12</td><td>0.31</td><td>1.31</td><td>29.30</td></tr>
<tr><td>Liver</td><td>0.11</td><td>0.54</td><td>1.14</td><td>27.43</td></tr>
<tr><td>Lymph node</td><td>0.09</td><td>0.73</td><td>1.27</td><td>70.16</td></tr>
<tr><td>Thymus</td><td>0.05</td><td>0.27</td><td>2.74</td><td>50.39</td></tr>
<tr><td>Pancreas</td><td>0.04</td><td>0.23</td><td>1.24</td><td>113.35</td></tr>
<tr><td>Pituitary gland</td><td>0.04</td><td>0.25</td><td>1.09</td><td>120.91</td></tr>
<tr><td>Esophagus wall</td><td>0.03</td><td>0.09</td><td>1.90</td><td>20.70</td></tr>
<tr><td>Stomach wall</td><td>0.03</td><td>0.14</td><td>1.22</td><td>11.44</td></tr>
<tr><td>Brain (whole)</td><td>0.01</td><td>0.01</td><td>0.28</td><td>0.95</td></tr>
</table></td></tr>
<tr><td>PK and bone marrow biodistribution assessment of ^{3}H-DSPC-labeled CPX-351 mini Applikon compared to non-liposomal formulations (Cytarabine/Daunorubicin) in CD-1 nude mice following a single i.v. treatment / Study Report CT832</td><td>Female CD-1 nude mice received an IV bolus dose of CPX-351 at 12 units/kg (12 mg/kg Cyt, 5.3 mg/kg DN) or a combination of 600 mg/kg Cyt and 9 mg/kg DN as the non-liposomal formulations. Plasma and bone marrow were collected up to 38 hours postdose.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
Plasma and bone marrow exposure of Cyt and DN after treatment with CPX-351
<table>
<tr><th rowspan="2">Parameter</th><th colspan="2">Total Cyt</th><th colspan="2">Total DN</th></tr>
<tr><th>Plasma</th><th>BM</th><th>Plasma</th><th>BM</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>221,230</td><td>1348</td><td>95,698</td><td>590</td></tr>
<tr><td>t_{max} (h)</td><td>0.25</td><td>1.0</td><td>0.25</td><td>2.0</td></tr>
<tr><td>AUC_{last} (ng/mL·hr)</td><td>2,232,549</td><td>13,454</td><td>872,432</td><td>12,852</td></tr>
<tr><td>CL (mL/h/kg)</td><td>5.24</td><td>-</td><td>6.00</td><td>-</td></tr>
<tr><td>$t_{1/2}$ (h)</td><td>6.58</td><td>14.5</td><td>5.74</td><td>21.4</td></tr>
</table>
Plasma and bone marrow exposure of Cyt and DN after treatment with non-liposomal formulations
<table>
<tr><th rowspan="2">Parameter</th><th colspan="2">Total Cyt</th><th colspan="2">Total DN</th></tr>
<tr><th>Plasma</th><th>BM</th><th>Plasma</th><th>BM</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>496,178</td><td>25,812</td><td>532</td><td>1,172</td></tr>
<tr><td>t_{max} (h)</td><td>0.25</td><td>0.25</td><td>0.25</td><td>0.5</td></tr>
<tr><td>AUC_{last} (ng/mL·hr)</td><td>399,158</td><td>23,495</td><td>1,001</td><td>10,554</td></tr>
<tr><td>CL (mL/h/kg)</td><td>1503</td><td>-</td><td>6869</td><td>-</td></tr>
<tr><td>$t_{1/2}$ (h)</td><td>0.35</td><td>0.52</td><td>1.99</td><td>7.51</td></tr>
</table>
</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Radioprofiling and Metabolite Identification in Rats after a Single Intravenous Bolus Dose of [^{14}C-Daun]CPX-351 and [^{3}H-Cyt]CPX-351 or Free [^{3}H]Cytarabine and Free [^{14}C]Daunorubicin or [^{14}C-Cyt]CPX-351 or Free [^{14}C]Cytarabine and Free Daunorubicin to Male and Female Sprague-Dawley Rats or Male Long-Evans Rats - Analytical Phase / Study Report (b) (4) 13692</td><td>Male and female bile duct-cannulated Sprague-Dawley rats received IV injections of ^{14}C-labeled CPX-351 or Cyt and DN as the non-liposomal formulations. Plasma, urine, feces, and/or bile were collected. Cyt→uracil arabinoside (AraU) and DN→daunorubicinol are the main systemic biotransformation pathways whether administered as CPX-351 or as the non-liposomal products.</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Pharmacokinetics, Mass Balance, and Biliary Excretion of [^{14}C] and [^{3}H] Following a Single Intravenous Bolus Dose of [^{14}C]CPX-351 and [^{3}H]CPX-351, or Free [^{3}H]Cytarabine and Free [^{14}C]Daunorubicin, to Male and Female Sprague-Dawley Rats

and

Pharmacokinetics, Mass Balance, and Biliary Excretion of [^{14}C] Following a Single Intravenous Bolus Dose of [^{14}C]CPX-351 Liposome Injection, or a Saline</td><td>
Excretion of ^{14}C-Cyt after administration of CPX-351 or non-liposomal Cyt in rats
<table>
<tr><th rowspan="2">Group</th><th colspan="5">Percent of administered dose</th></tr>
<tr><th>Bile</th><th>Urine</th><th>Feces</th><th>Cage rinse / wash</th><th>Total</th></tr>
<tr><td>CPX-351 (BDC)</td><td>0.40</td><td>83.61</td><td>0.80</td><td>11.61</td><td>96.42</td></tr>
<tr><td>Non-liposomal (BDC)</td><td>0.66</td><td>90.18</td><td>0.88</td><td>8.47</td><td>100.19</td></tr>
</table>
BDC: bile duct-cannulated.
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Solution of Free [^{14}C]Cytarabine and Free Daunorubicin, to Male and Female Sprague-Dawley Rats</td><td>
Excretion of ^{14}C-DN after administration of CPX-351 or non-liposomal DN in rats
<table>
<tr><th rowspan="2">Group</th><th colspan="6">Percent of administered dose</th></tr>
<tr><th>Bile</th><th>Urine</th><th>Feces</th><th>Cage rinse / wash</th><th>Carcass</th><th>Total</th></tr>
<tr><td>CPX-351 (intact)</td><td>ND</td><td>9.32</td><td>76.14</td><td>2.56</td><td>2.28</td><td>90.30</td></tr>
<tr><td>CPX-351 (BDC)</td><td>45.52</td><td>6.76</td><td>3.08</td><td>1.32</td><td>ND</td><td>56.69</td></tr>
<tr><td>Non-liposomal (BDC)</td><td>61.57</td><td>20.44</td><td>4.93</td><td>2.09</td><td>ND</td><td>89.03</td></tr>
</table>
BDC: bile duct-cannulated; ND: not determined.
</td></tr>
<tr><td>TK data from general toxicology studies</td><td>
2-Cycle rat study / Study Report 1005-0361
AUC of Cyt and DN after first and third doses of CPX-351
<table>
<tr><th rowspan="2">CPX-351 dose level*</th><th colspan="2">Cyt AUC$_{(0\text{-}inf)}$ (ng*hr/mL)</th><th colspan="2">DN AUC$_{(0\text{-}inf)}$ (ng*hr/mL)</th></tr>
<tr><th>Day 1</th><th>Day 5</th><th>Day 1</th><th>Day 5</th></tr>
<tr><td>5 mg/kg</td><td>1,450,588</td><td>1,401,068</td><td>546,231</td><td>862,409</td></tr>
<tr><td>10 mg/kg</td><td>3,219,156</td><td>3,767,029</td><td>1,388,477</td><td>1,416,842</td></tr>
</table>
*CPX-351 dose levels are presented based on Cyt.

2-Cycle dog study / Study Report 1005-0372
AUC of Cyt and DN after first and third doses of CPX-351
<table>
<tr><th rowspan="2">CPX-351 dose level*</th><th colspan="2">Cyt AUC$_{(0\text{-}inf)}$ (ng*hr/mL)</th><th colspan="2">DN AUC$_{(0\text{-}inf)}$ (ng*hr/mL)</th></tr>
<tr><th>Day 1</th><th>Day 5</th><th>Day 1</th><th>Day 5</th></tr>
<tr><td>1 mg/kg</td><td>145,195</td><td>116,966</td><td>76,714</td><td>64,932</td></tr>
<tr><td>2 mg/kg</td><td>402,953</td><td>455,392</td><td>203,328</td><td>200,600</td></tr>
<tr><td>3 mg/kg</td><td>725,988</td><td>1,100,223</td><td>407,164</td><td>453,852</td></tr>
</table>
*CPX-351 dose levels are presented based on Cyt.
</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

A Two-Cycle Intravenous Infusion Toxicity Study Followed by a 28-Day Recovery Period in Sprague-Dawley Rats / Study Report 1005-0361

Key Study Findings

- Moribundity and mortality observed at the ≥10 mg/kg dose levels was associated with hypocellularity of the bone marrow and lymphoid organs.
- Hematological toxicity at the 5 mg/kg dose level was consistent with the expected toxicity profiles for Cyt and DN.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Test article was administered Q2D x 3, in a 3 week cycle (Days 1, 3, 5 and Days 22, 24, 26).

Experimental design

Group	Treatment	CPX-351 dose level#	Number of animals					
			Main		Recovery		TK	
			M	F	M	F	M	F
1	Control article	0 mg/kg	10	10	5	5	0	0
2 (LD)	Low dose CPX-351	5 mg/kg	10	10	0	0	9	9
3 (MD)	Mid dose CPX-351	10 mg/kg	10	10	0	0	9	9
4* (HD)	High dose CPX-351	15 mg/kg	10	10	5	5	0	0
		10 mg/kg	0	0	15	15	0	0

CPX-351 dose levels are presented based on Cyt; * The dose level for Group 4 was reduced (15→10 mg/kg) mid study due to the severity of clinical signs.

Route of administration: IV infusion (1 hour)

Formulation/Vehicle: 0.9% Sodium Chloride for Injection USP

Species/Strain: Rat / Sprague Dawley

Number/Sex/Group: See table above

Age: 8 to 9 weeks

Satellite groups/unique design: TK group

Deviation from study protocol affecting interpretation of results: Yes; the dose level for Group 4 was reduced mid study due to the severity of clinical signs. Surviving animals were reassigned as Recovery animals. The change in dose level occurred on different study days for each replicate.

Impact of in-study changes to the experimental design

Replicate*	Number of doses received per dose level	
	Number of doses at 15 mg/kg	Number of doses at 10 mg/kg
A	2 (Day 1, 3)	1 (Day 5)
B	2 (Day 1, 3)	1 (Day 5)
C	1 (Day 1)	2 (Day 3, 5)
D	1 (Day 1)	2 (Day 3, 5)

* Animals were allocated to different replicates to permit dosing on consecutive days.

Observations and results: changes from control

Parameters	Major findings
Mortality	Summary of mortality

Sex	Male				Female			
Group	Control	5 mg/kg	10 mg/kg	15 mg/kg	Control	5 mg/kg	10 mg/kg	15 mg/kg
n	15	10	10	15	15	10	10	15
Number of deaths	1*	1*	8	15	0	3*	7	15
Day of study	3	9	3-33	10-15	---	8,21,24	8-32	8-16

*Deaths in the control and 5 mg/kg groups were not considered drug-related.

Clinical signs

MD/HD: decreased grooming and piloerection, partial or complete ptosis, decreased activity, hunched back position, pallor, dehydration, reduced or absent righting reflex, increased or labored respiration, and changes in the consistency and/or color of feces.

Body weights (on Day 34)

LD: ↓17% (M)
MD: not determined (only 2M/3F surviving)
HD: not applicable (none surviving)

Ophthalmoscopy

Unremarkable

Hematology

% Mean differences vs. concurrent controls (Day 34)

Parameter	Males			Females		
	Dose level (mg/kg)			Dose level (mg/kg)		
	5	10	15	5	10	15
n	8	1	0	7	1	0
WBC	-59%	-88%	---	-46%	-22%	---
NEUT	-26%	-67%	---	+3%	+679%	---
LYM	-72%	-87%	---	-60%	-31%	---
MONO	-33%	-78%	---	-31%	+206%	---
RBC	-25%	-49%	---	-22%	-53%	---
HGB	-19%	-35%	---	-16%	-45%	---
HCT	-17%	-32%	---	-17%	-43%	---
PLT	-60%	-92%	---	-49%	-71%	---
RETIC	-18%	-87%	---	+84%	+164%	---
PT	-4%	-2%	---	-6%	+1%	---
APTT	-10%	-9%	---	-10%	-11%	---

Clinical chemistry

% Mean differences vs. concurrent controls (Day 34)

Parameter	Males			Females		
	Dose level (mg/kg)			Dose level (mg/kg)		
	5	10	15	5	10	15
n	9	1	0	7	3	0
ALB	-8%	-11%	---	-3%	-34%	---
TP	-5%	-11%	---	-5%	-18%	---
ALT	+72%	+7%	---	-30%	+110%	---
ALP	+60%	+6%	---	+125%	-11%	---
CHOL	+22%	+44%	---	+19%	+88%	---
TRIG	+70%	+123%	---	+14%	+21%	---

Urinalysis

Unremarkable

Gross pathology

LD: thymus (small), iliac lymph node (enlargement).
MD: thymus (small), spleen (small), testes (dark discoloration/area), adrenals (enlargement).
HD: thymus (small), spleen (small), testes (dark discoloration/area), adrenals (enlargement), epididymides (dark area).

Organ weights

% Mean difference vs. concurrent controls (scheduled sacrifice)

Organ	Males			Females		
	Dose level (mg/kg)			Dose level (mg/kg)		
	5	10	15	5	10	15
n	9	2	0	7	3	0
Pituitary	-15% (3%)	-17% (-3%)	---	---	---	---
Prostate	-19% (0)	-37% (-27%)	---	---	---	---
Spleen	-24% (-4%)	-47% (-39%)	---	-23% (-23%)	-16% (-7%)	---
Testes	-23% (-7%)	-34% (-25%)	---	---	---	---
Thymus	-69% (-64%)	-75% (-70%)	---	-50% (-51%)	-80% (-77%)	---

Absolute (% of body weight)

Histopathology
Adequate battery: Yes

LD/MD: minimal to severe hematopoietic hypocellularity of the bone marrow of the sternum and femur; minimal to severe lymphoid hypocellularity/atrophy of the spleen, thymus, and lymph nodes.
HD: marked to severe hematopoietic hypocellularity of the bone marrow of the sternum and femur; minimal to severe lymphoid hypocellularity/atrophy of the spleen, thymus, and lymph nodes; mild to moderate single cell cryptal epithelium

	necrosis of the small intestinal mucosa; minimal to moderate single cell glandular epithelium necrosis of the large intestinal mucosa.
Blood copper concentration analysis	A slight dose-related increase in blood copper concentration was observed; levels trended towards baseline by 7 days after the last dose.

Summary of blood copper concentration analysis

Group	Day	n	Mean (µg/mL)	Standard deviation (µg/mL)	Range (µg/mL)
1	34	29	1.28	0.31	0.85-2.35
	56	10	1.05	0.20	0.79-1.47
2 (LD)	34	16	1.64	0.41	1.09-2.36
3 (MD)	3	1	10.98	---	---
	8-14	6	1.78	0.46	1.20-2.38
	16-25	2	2.46	1.15	1.65-3.28
	33-34	7	2.15	0.63	1.33-3.09
4 (HD)	10-16	18	2.31	0.81	1.30-4.47

LD: low dose; MD: mid dose; HD: high dose.

A Two-Cycle Intravenous Infusion Toxicity Study in Beagle Dogs Followed by a 28-Day Recovery Period / Study Report 1005-0372

Key Study Findings

- Moribundity and mortality observed at the ≥2 mg/kg dose levels was associated with hypocellularity of the bone marrow and lymphoid organs and necrosis of the small and large intestines.
- Hematological and enteric toxicity was consistent with the expected toxicity profiles for Cyt and DN.
- The myelosuppression observed in animals treated with CPX-351, but not with equivalent doses of free Cyt and DN, suggests liposomal encapsulation is important to the biological activity of CPX-351.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Test article was administered Q2D x 3, in a 3 week cycle (Days 1, 3, 5 and Days 22, 24, 26).

Experimental design

Group	Treatment	CPX-351 dose level#	Number of animals			
			Main		Recovery	
			M	F	M	F
1	Control article*	0 mg/kg	3	3	2	2
2	Vehicle$	0 mg/kg	3	3	0	0
3 (LD)	CPX-351	1 mg/kg	3	3	0	0
4 (MD)	CPX-351	2 mg/kg	1	1	2	2

5 (HD)	CPX-351	3 mg/kg	3	3	2	2
6	Comparative control[@]	2 mg/kg	3	3	0	0

[#] CPX-351 dose levels are presented based on Cyt; * Control animals received 0.9% sodium chloride for injection USP; [$] Vehicle animals received liposomes containing no drug; [@] Comparative control animals received both free Cyt and DN at doses equivalent to the mid dose level of CPX-351.

Route of administration: IV infusion (1 hour)

Formulation/Vehicle: 0.9% Sodium Chloride for Injection USP / Empty copper-containing liposomes

Species/Strain: Dog / Beagle

Number/Sex/Group: See table above

Age: 8 to 9 months

Satellite groups/unique design: None

Deviation from study protocol affecting interpretation of results: Yes; due to the severity of clinical signs only one cycle was administered to animals in Groups 4 and 5. Surviving Group 4 animals were re-assigned as recovery animals.

Observations and Results: changes from control

Parameters | **Major findings**

Mortality

Summary of mortality

Sex	Male						Female					
Group	C*	V[$]	LD	MD	HD	CD[@]	C*	V[$]	LD	MD	HD	CD[@]
n	5	3	3	3	5	3	5	3	3	3	5	3
Number of deaths	0	0	0	1	5	0	0	0	0	1	5	0
Day of study	-	-	-	12	7-10	-	-	-	-	12	7-9	-

* 0.9% sodium chloride for injection control; [$] liposomes containing no drug; [@] 2 mg/kg Cyt + 0.88 mg/kg DN (free drugs).

Clinical signs: **MD/HD:** decreased activity, dehydration, thin body condition, emesis, and changes in the consistency and/or color of feces.

Body weights: Unremarkable

Ophthalmoscopy: Unremarkable

ECG: Unremarkable

Hematology

% Mean differences vs. concurrent controls (Day 33)

Sex	Male					Female				
Group	V[$]	LD	MD	HD	CD[@]	V[$]	LD	MD	HD	CD[@]
n	3	3	2	0	3	3	3	2	0	3
WBC	0	-66%	-14%	---	-60%	+3%	-46%	-11%	---	-56%
RBC	+8%	-8%	-2%	---	-9%	+5%	-14%	-11%	---	-14%
HGB	+7%	-10%	-3%	---	-13%	+8%	-13%	-10%	---	-12%
HCT	+10%	-7%	+2%	---	-10%	+4%	-13%	-9%	---	-13%
NEUT	-4%	-79%	-7%	---	-95%	+7%	-58%	+7%	---	-91%
LYM	+7%	-42%	-26%	---	-6%	-3%	-27%	-42%	---	-22%
RETIC	-19%	+15%	+96%	---	+415%	-16%	-29%	+73%	---	+61%

[$] Liposomes containing no drug; [@] 2 mg/kg Cyt + 0.88 mg/kg DN (free drugs).

<table>
<tr><td></td><td>
% Mean differences vs. concurrent controls (recovery Day 22)
<table>
<tr><th>Sex</th><th>Male</th><th>Female</th></tr>
<tr><th>Group</th><th>MD</th><th>MD</th></tr>
<tr><td>n</td><td>2</td><td>2</td></tr>
<tr><td>WBC</td><td>-24%</td><td>-25%</td></tr>
<tr><td>RBC</td><td>-5%</td><td>-2%</td></tr>
<tr><td>HGB</td><td>-3%</td><td>-3%</td></tr>
<tr><td>HCT</td><td>0</td><td>-2%</td></tr>
<tr><td>NEUT</td><td>-23%</td><td>-29%</td></tr>
<tr><td>LYM</td><td>-22%</td><td>-13%</td></tr>
<tr><td>RETIC</td><td>+111%</td><td>+59%</td></tr>
</table>
</td></tr>
<tr><td>Clinical chemistry</td><td>Unremarkable</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross pathology</td><td>Unremarkable</td></tr>
<tr><td>Organ weights</td><td>
% Mean difference vs. concurrent controls (scheduled sacrifice)
<table>
<tr><th rowspan="3">Organ</th><th colspan="5">Males</th><th colspan="5">Females</th></tr>
<tr><th colspan="5">Group</th><th colspan="5">Group</th></tr>
<tr><th>V$</th><th>LD</th><th>MD</th><th>HD</th><th>CD@</th><th>V$</th><th>LD</th><th>MD</th><th>HD</th><th>CD@</th></tr>
<tr><td>n</td><td>3</td><td>3</td><td>0</td><td>0</td><td>3</td><td>3</td><td>3</td><td>0</td><td>0</td><td>3</td></tr>
<tr><td>Adrenal</td><td>-11%
(-11%)</td><td>+10%
(+22%)</td><td>---</td><td>---</td><td>+13%
(+22%)</td><td>---</td><td>---</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td>Liver</td><td>-2%
(+4%)</td><td>-6%
(+11%)</td><td>---</td><td>---</td><td>-5%
(+9%)</td><td>---</td><td>---</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td>Lung</td><td>-2%
(+4%)</td><td>-7%
(+10%)</td><td>---</td><td>---</td><td>+5%
(+21%)</td><td>---</td><td>---</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td>Spleen</td><td>-15%
(-9%)</td><td>+18%
(+39%)</td><td>---</td><td>---</td><td>+21%
(+39%)</td><td>+33%
(+29%)</td><td>-14%
(-15%)</td><td>---</td><td>---</td><td>-28%
(-28%)</td></tr>
<tr><td>Testes</td><td>-12%
(-6%)</td><td>-22%
(-9%)</td><td>---</td><td>---</td><td>-42%
(-35%)</td><td>---</td><td>---</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td>Thymus</td><td>-14%
(+19%)</td><td>-23%
(-10%)</td><td>---</td><td>---</td><td>-23%
(-14%)</td><td>-30%
(-31%)</td><td>-29%
(-31%)</td><td>---</td><td>---</td><td>-52%
(-52%)</td></tr>
<tr><td>Uterus</td><td>---</td><td>---</td><td>---</td><td>---</td><td>---</td><td>+328%
(+260%)</td><td>-1%
(-5%)</td><td>---</td><td>---</td><td>-4%
(-10%)</td></tr>
</table>
Absolute (% of body weight); $ liposomes containing no drug; @ 2 mg/kg Cyt + 0.88 mg/kg DN (free drugs).
</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>MD/HD: severe hematopoietic hypocellularity of the bone marrow of the sternum and femur; mild to severe necrosis, hypocellularity, and/or atrophy of the spleen, thymus, and lymph nodes; mild to severe single cell cryptal epithelium necrosis of the small intestinal mucosa; marked to severe single cell glandular epithelium necrosis of the large intestinal mucosa.

At recovery: unremarkable at all doses.</td></tr>
<tr><td>Blood copper concentration analysis</td><td>Copper levels were at baseline 1 week after the last dose; earlier time points were not assessed.</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.

5.5.2. Genetic Toxicology

No genotoxicity studies were conducted with CPX-351. The Applicant references the known genotoxic effects of the listed drugs DepoCyt® and DaunoXome®. According to the labels for DepoCyt® and DaunoXome®, both Cyt and DN were mutagenic in vitro and clastogenic in vitro and in vivo. Cyt caused the transformation of hamster embryo cells and rat H43 cells in vitro.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with CPX-351 per ICH S9. The Applicant references the known effects of the listed drugs DepoCyt® and DaunoXome®. According to the label for DaunoXome®, DN produced a high incidence of mammary tumors in rats.

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted with CPX-351 per ICH S9. The Applicant references the known effects of the listed drugs DepoCyt® and DaunoXome®. According to the label for DepoCyt®, Cyt was teratogenic in mice and rats, and embryotoxic in mice. Cyt was clastogenic and caused an increase in sperm-head abnormalities in mice. According to the label for DaunoXome®, DN was embryotoxic in rats and impaired the fertility in male dogs.

5.5.5. Other Toxicology Studies

Assessment of Impurities

Seven CPX-351 drug product impurities (b) (4) the qualification threshold[5]. The Applicant's justification to qualify these impurities is in Table 4. Of note, the Certificates of Analysis for the CPX-351 drug product batches administered in the animal studies do not list impurity levels. The nonclinical reviewer concurs with the Applicant's justification to qualify the CPX-351 drug product impurities.

Table 4: CPX-351 drug product impurities exceeding the ICH Q3B(R2) qualification threshold

Impurity	Current acceptance criteria	Proposed acceptance criteria	Highest level in CPX-351 clinical study batches	Applicant's justification for proposed limit
Uracil arabinoside (AraU)	NMT 0.3% (USP)	NMT (b) (4)%	(b) (4)%	AraU is a degradation product and inactive metabolite of cytarabine. AraU was present as a metabolite in the plasma following nonclinical and clinical IV administration of CPX-351.
Daunorubicinol	NMT 1.5% (Ph Eur)	NMT (b) (4)%	(b) (4)%	Daunorubicinol is the active metabolite of daunorubicin. Daunorubicinol was present as a metabolite in the plasma following nonclinical and clinical IV administration of CPX-351.

[5] FDA Guidance for Industry, 2006, Q3B(R2) Impurities in New Drug Products

Impurity	Current acceptance criteria	Proposed acceptance criteria	Highest level in CPX-351 clinical study batches	Applicant's justification for proposed limit
Daunorubicin aglycone	NMT 0.5% (Ph Eur)	NMT (b) (4)%	(b) (4)%	Daunorubicin aglycone is a degradation product and inactive metabolite of daunorubicin.
Doxorubicin	NMT 0.5% (Ph Eur)	NMT (b) (4)%	(b) (4)%	Doxorubicin is the API in Doxil®, an FDA-approved liposomal doxorubicin hydrochloride product labeled for the treatment of ovarian cancer.
(b) (4)	N/A	NMT (b) (4)%	(b) (4)%	(b) (4) is an endogenous substance, present in the plasma of healthy subjects at concentration of ~300 uM
(b) (4)	N/A	NMT (b) (4)%	≤ (b) (4)%	(b) (4)
(b) (4)	N/A	NMT (b) (4)%	(b) (4)%	

NMT: not more than; USP: United States Pharmacopeia; Ph Eur: European Pharmacopoeia; N/A: not applicable.

Michael L. Manning, PhD
Primary Reviewer

Christopher Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The key review questions focus on the appropriateness of the dose, recommendations for the administration of CPX-351 in patients with renal impairment and the acceptability of including patients less than 60 years in the indication.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209401. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Evidence of effectiveness	A randomized Phase III trial provides primary evidence. Exposure-response relationship for OS provides supportive evidence.
General Dosing instructions	A dose of 44 mg of daunorubicin and 100 mg of cytarabine per m^2 via intravenous infusion over 90 minutes or more on days 1, 3, and 5 for the first induction and on days 1 and 3 for the second course of induction if needed, and a dose of 29 mg/65 mg per m^2 on days 1 and 3 for the courses of consolidation is effective and appears to be safe.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The dosage regimen based on body surface area (BSA) was supported by significant effect of BSA on all PK parameters in the population PK analysis. No dose modification is needed for specific populations of age, sex, race, body weight, body mass index, white blood cell count and mild hepatic impairment. These factors were not found as a significant covariate on PK parameters. A PMR regarding moderate and severe renal impairment will be issued, because these patients may require a modified dose. Patients with severe renal impairment were not enrolled in the clinical trials and higher exposures, as well as greater TEAEs, were observed in patients with moderate renal impairment compared to patients with normal renal function.

The issued Post-Marketing Requirement (PMR) is summarized below:

PMC or PMR	Key Issue to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☑ PMR	Effect of renal impairment on PK	Cytarabine is primarily excreted in the urine; and a dose reduction by 50% for creatinine >3 mg/dL is recommended per non-liposome daunorubicin labeling. Around 40% increase in exposures of total	(b) (4)

		daunorubicin and cytarabine as well as greater TEAEs Grade 3 to 5, serious TEAEs and TEAEs leading to death were observed in patients with moderate renal impairment compared to those in patients with normal renal function. In addition, the effect of severe renal impairment on CPX-351 PK, efficacy and safety has not been tested in the trial.	(b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Following the administration of a dose of 44 mg/100 mg per m^2 administered as a 90-minute intravenous infusion on days 1, 3, and 5, the mean [%coefficient of variation (CV)] maximum plasma concentrations (C_{max}) on Day 5 for daunorubicin was 26.0 (32.7%) mcg/mL and cytarabine was 62.2 (33.7%) mcg/mL. The mean (%CV) area under the curve (AUC) during one dosing interval for daunorubicin was 637 (38.4%) mcg·h/mL and cytarabine was 1900 (44.3%) mcg·h/mL. The PK parameters, clearance, volume of distribution and terminal half-life for daunorubicin and cytarabine were nearly similar because more than 99% of the daunorubicin and cytarabine in the circulation remains trapped within the liposomes.

The accumulation ratio was 1.3 for daunorubicin and 1.4 for cytarabine. There was no evidence of time-dependent kinetics or major departures from dose proportionality over the range of 1.3 mg/3 mg per m^2 to 59 mg/134 mg per m^2.

Distribution
The volume of distribution (%CV) is 6.6 L (36.8%) for daunorubicin and 7.1 L (49.2%) for cytarabine. Plasma protein binding is 97% for daunorubicin and 13% for cytarabine per labeling of non-liposomal formulations.

Elimination
The half-life (%CV) for daunorubicin is 31.5 h (28.5%) and for cytarabine is 40.4 h (24.2%). The clearance (%CV) is 0.16 L/h (53.3%) for daunorubicin and 0.13 L/h (60.2%) for cytarabine.

Metabolism
Subsequent to release from liposomes, daunorubicin is catalyzed by aldoketo reductase and carbonyl reductase enzymes to the active metabolite daunorubicinol. Cytarabine is metabolized by cytidine deaminase to the inactive metabolite 1-β-D-arabinofuranosyluracil (AraU).

Excretion
Urinary excretion of daunorubicin and daunorubicinol account for 9% of the administered dose of daunorubicin, and urinary excretion of cytarabine and AraU account for 70% of the administered dose of cytarabine.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposes a dose of 44 mg/100 mg per m^2 via intravenous infusion over 90 minutes or more on days 1, 3, and 5 for the first induction and on days 1 and 3 for the second course of induction if needed, and a CPX-351 dose of 29 mg/65 mg per m^2 on days 1 and 3 for the courses of consolidation. CPX-351 at the proposed dosing regimen evaluated in Trial 301 was effective and appeared to be safe in patients with newly diagnosed AML (n = 153). The population PK analysis supports dosing individualization based on BSA.

Therapeutic Individualization

Renal Impairment: Cytarabine is primarily excreted in the urine; and a dose reduction by 50% for patients with creatinine >3 mg/dL is recommended per non-liposome daunorubicin labeling. A dedicated renal impairment trial has not been conducted for CPX-351. The population PK analysis suggests that mild to moderate renal impairment [CL_{CR} 30 mL/min to 89 mL/min, as estimated by Cockcroft-Gault (C-G)] had no clinically significant effect on the exposure of total daunorubicin and cytarabine, supporting no dose adjustment for patients with mild or moderate renal impairment. The potential effects of severe renal impairment (CL_{CR} 15 mL/min to 29 mL/min, C-G) and end-stage renal disease on the PK of daunorubicin and cytarabine administered as CPX-351 are unknown. The population PK analysis showed that dosing individualization is not needed for other factors, e.g. age, sex, race, body weight, body mass index, and white blood cell count after adjusting dose by BSA.

Outstanding Issues

One PMR will be issued for a moderate and severe renal impairment trial.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The summary of clinical pharmacology, pharmacokinetics and ADME information of CPX-351 is listed below.

Pharmacology	
Mechanism of Action	Daunorubicin is an anthracycline topoisomerase inhibitor per previous characterization of MoA in the published literatures (Belloc et al. 1992, Gewirtz 1999, and Fried et al. 1982). Cytarabine is a cell cycle phase-specific nucleoside metabolic inhibitor per FDA's approved cytarabine liposome injection (DepoCyt®).
Active Moieties	Daunorubicin and cytarabine are the active moieties with a fixed 1:5 molar ratio in the nano-scale liposomal formulation of VYXEOS
QT Prolongation	VYXEOS has low risk of QT interval prolongation.

General Information	
Bioanalysis	Daunorubicin and its active metabolite daunorubicinol, as well as cytarabine and its inactive metabolite 1-β-D-arabinofuranosyluracil (Ara-U) were measured using validated LC/MS/MS methods.
Drug total exposure at steady state following the therapeutic dosing regimen	The mean (SD) C_{max} for daunorubicin was 26.0 (8.5) mcg/mL and cytarabine was 62.2 (20.9) mcg/mL, and the mean (SD) AUC during one dosing interval for daunorubicin was 637 (244) mcg·h/mL and cytarabine was 1900 (844) mcg·h/mL on Day 5 in adult patients who received a dose of 44 mg/100 mg per m^2 administered as a 90-minute IV infusion on days 1, 3, and 5.
Minimal effective dose or exposure	Induction period: 44 mg/100 mg per m^2 Consolidation period: 29 mg/65 mg per m^2
Dose Proportionality	Daunorubicin and cytarabine exposure increase proportionally over the VYXEOS dose range of 1.3 mg/3 mg per m^2 to 59 mg/134 mg per m^2.
Accumulation	The accumulation ratio was 1.3 for daunorubicin and 1.4 for cytarabine.
Variability	The %CV of C_{max} for daunorubicin was 32.7% and cytarabine was 33.7%. The %CV of AUC during one dosing interval for daunorubicin was 38.4% and cytarabine was 44.3%.
Distribution	
Volume of Distribution	The volume of distribution (%CV) was 6.6 L (36.8%) for daunorubicin and 7.1 L (49.2%) for cytarabine.
Plasma Protein Binding	Plasma protein binding is 97% for daunorubicin and 13% for cytarabine per labeling for non-liposomal formulations.
Blood to Plasma Ratio	Not evaluated
Substrate transporter	Daunorubicin is known to be a substrate of P-glycoprotein per literature.
Elimination	
Mean terminal elimination half-life	The half-life (CV%) for daunorubicin was 31.5 h (28.5%) and cytarabine was 40.4 h (24.2%).
Metabolism	
Primary metabolic pathway(s)	Subsequent to release from the liposomes, daunorubicin is catalyzed by aldoketo reductase and carbonyl reductase enzymes to the active metabolite daunorubicinol. The cytarabine is metabolized by cytidine deaminase to the inactive metabolite 1-β-D-arabinofuranosyluracil (AraU).
Inhibitor/Inducer	Not evaluated
Excretion	
Primary excretion pathways (% dose) ± SD	Following administration of VYXEOS, urinary excretion of cytarabine and AraU accounted for approximately 70% of the administered dose of cytarabine, and urinary excretion of daunorubicin and daunorubicinol accounted for approximately 9% of the administered dose of daunorubicin.

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed CPX-351 dosing regimen had superior efficacy with similar safety profile compared to 7 + 3 standard of care in adult patients with newly diagnosed AML in Trial 301. The maximum tolerated dose (MTD) was identified as 44 mg/100 mg per m^2 in the dose-escalation Trial 101, and the MTD was subsequently used for both induction and consolidation periods in Trials 204 and 205. However, severe thrombocytopenia was observed in the consolidation courses at MTD in both trials. Therefore, a reduced dose of 29 mg/65 mg per m^2 was selected for consolidation in Trial 206 and Trial 301, because this dose level was about twice the dose level needed to achieve the first complete response in Trial 101. The exposure-response (E-R) analyses for both efficacy and safety support the proposed induction dose based on the area under the plasma concentration-time curve from 0-48 hours (AUC_{0-48h}) after the Day 5 dose of CPX-351 44 mg/100 mg per m^2 in the first induction. Refer to Appendix 13.4.4 for more details on the exposure-response analysis. The safety data from Trials 206 and 301 supports the dose of 29 mg/65 mg per m^2 for consolidation phase.

Efficacy: CPX-351 demonstrated superiority in the primary efficacy endpoint OS, 32.0% vs. 15.4%, when compared to the 7 + 3 standard of care in Trial 301 (**Figure 5**). The median survival for the CPX-351 treatment group was 9.6 months compared to 6.0 months for the 7 + 3 treatment group (Hazard Ratio = 0.69, 95% confidence interval [CI] = 0.52, 0.90, 1-sided log-rank test p = 0.003).

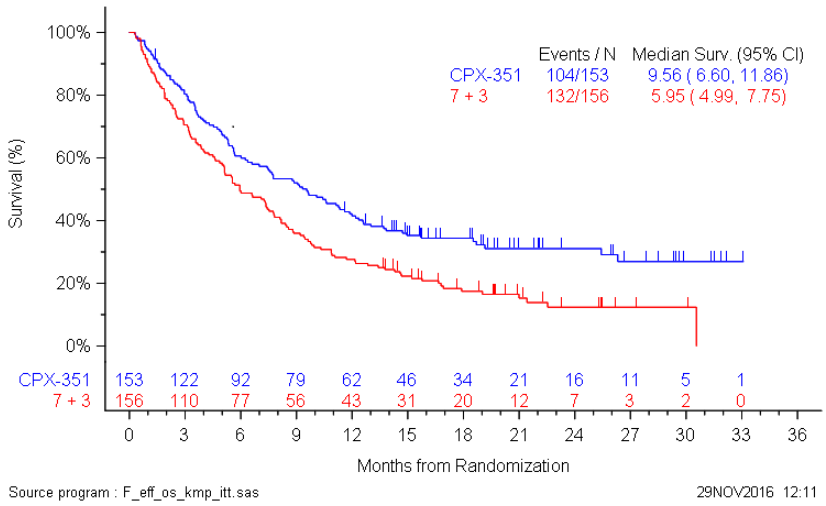


Figure 5: Kaplan-Meier Curve of Overall Survival for the ITT Population in Trial 301.
Source: Trial 301 clinical study report Figure 14.2.1.2.1.

The Kaplan-Meier analysis of the E-R relationship for OS showed that lower exposures (AUC_{0-48h} after day 5 dose of the first induction) of total daunorubicin and cytarabine tended to result in

smaller OS in the range of exposures observed in the ER efficacy population (n = 130) who received CPX-351 at the proposed dosing regimen in Trial 301 (**Figure 6**).

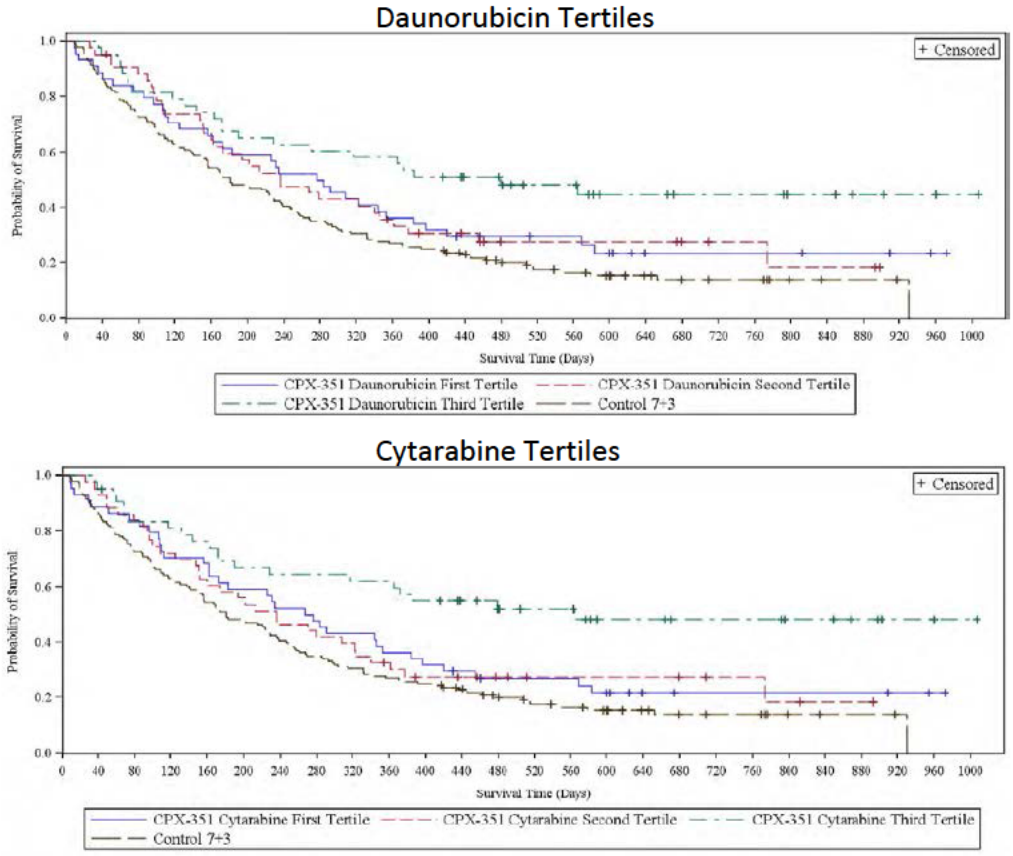


Figure 6: Kaplan-Meier Analysis of Overall Survival for the ER (Plasma Exposure) Efficacy Population in Trial 301.
Source: CPX-351 exposure-response report Figure 3 and Figure 4.

Safety: The MTD was determined as 44 mg/100 mg per m^2 for CPX-351 in the dose-escalation Trial 101. CPX-351 44 mg/100 mg per m^2 for induction and 29 mg/65 mg per m^2 for consolidation appeared to be well tolerated and had comparable safety profile to 7 + 3 standard of care in the pooled safety population from Trials 101, 204, 205, 206 and 301 (**Table 5**). Although serious TEAEs were slightly higher following administration of CPX-351 at proposed dosing regimen compared with control treatment in both induction (38.7% v 32.2%) and consolidation (48.1% v 42.6%) periods, TEAEs leading to death were consistent between two treatment arms.

The E-R analysis for safety was conducted by comparing the safety profiles between the 7 + 3 standard of care arm and three exposure ($AUC_{0\text{-}48h}$ on Day 5) tertiles of total cytarabine in CPX-351 arm in Trial 301, because AUCs for daunorubicin and cytarabine were highly correlated. As shown in Table 6, there was no notable E-R relationship for most of the safety endpoints, except an apparent trend for the incidence of any grade 3-5 TEAEs in the first (86.5%), second (94.3%), and third (98.0%) cytarabine tertiles. However, TEAEs leading to death for CPX-351 in

the 3 cytarabine tertiles were less than 7 + 3 standard of care, and were not associated with total CPX-351 exposure.

Compared the 7 + 3 standard of care, CPX-351 treatment group had similar percentage of patients with TEAEs leading to dose held, reduced or interrupted (0.7%-5.2% vs. 0.7%-6.6%) and similar percentage of patients with TEAEs leading to treatment discontinuation (1.9% vs. 1.3%) in all induction and consolidation periods. Overall, CPX-351 had an acceptable safety profile in patients with newly diagnosed AML at proposed dosing regimen.

Table 5: Overall Summary of Treatment Emergent Adverse Events (Pooled Safety Population).

	Number of subjects, n (%)						
	Induction Period		Consolidation Period[a]			Treatment Period	
	CPX-351 100 units/m^2 N = 375	All Controls N = 236	CPX-351 65 units/m^2 N = 52	CPX-351 100 units/m^2 N = 63	All Controls N = 55	CPX-351 N = 375	All Controls N = 236
Any TEAEs[b]	375 (100)	236 (100)	44 (84.6)	61 (96.8)	49 (89.1)	375 (100)	236 (100)
TEAEs by Maximum NCI-CTC Grade[c]	375 (100)	236 (100)	44 (84.6)	61 (96.8)	49 (89.1)	375 (100)	236 (100)
Grade 1	2 (0.5)	4 (1.7)	12 (23.1)	6 (9.5)	5 (9.1)	2 (0.5)	4 (1.7)
Grade 2	31 (8.3)	21 (8.9)	4 (7.7)	9 (14.3)	14 (25.5)	27 (7.2)	20 (8.5)
Grade 3	251 (66.9)	158 (66.9)	20 (38.5)	36 (57.1)	17 (30.9)	239 (63.7)	150 (63.6)
Grade 4	63 (16.8)	28 (11.9)	7 (13.5)	5 (7.9)	9 (16.4)	73 (19.5)	33 (14.0)
Grade 5	28 (7.5)	25 (10.6)	1 (1.9)	5 (7.9)	4 (7.3)	34 (9.1)	29 (12.3)
Grade 3 to 5	342 (91.2)	211 (89.4)	28 (53.8)	46 (73.0)	30 (54.5)	346 (92.3)	212 (89.8)
TEAEs by Closest Relationship[d]							
Not related	13 (3.5)	16 (6.8)	8 (15.4)	12 (19.0)	10 (18.2)	12 (3.2)	16 (6.8)
Related	362 (96.5)	220 (93.2)	36 (69.2)	49 (77.8)	39 (70.9)	363 (96.8)	220 (93.2)
Serious TEAEs	145 (38.7)	76 (32.2)	25 (48.1)	33 (52.4)	24 (43.6)	189 (50.4)	91 (38.6)
TEAEs leading to discontinuation	7 (1.9)	3 (1.3)	0	0	0	7 (1.9)	3 (1.3)
TEAEs leading to death	28 (7.5)	25 (10.6)	1 (1.9)	5 (7.9)	4 (7.3)	34 (9.1)	29 (12.3)

Abbreviations: AE = adverse event; NCI-CTC = National Cancer Institute Common Terminology Criteria; SAE = serious adverse event; TEAE = treatment emergent adverse event.

[a] The CPX-351 65 units/m^2 consolidation dose was tested in Study 206 and Study 301. The CPX-351 100 units/m^2 consolidation dose was tested in Study 101 (101 units/m^2), Study 204, and Study 205.

[b] For SAEs or AEs identified as a bleeding event, a cardiac event, infection or rash, a TEAE is defined as an AE that started after the first dose of induction 1. For all other AEs, a TEAE is defined as an AE that started after the first dose of induction 1 and not more than 30 days after the last dose date.

[c] If a subject experiences an AE with more than one NCI-CTC grade, the subject is counted only once in maximum grade category.

Source: Integrated Summary of Safety Table 10.

Table 6: Overall Summary of Treatment Emergent Adverse Events – ER (Plasma Exposure) Safety Population (Cytarabine Tertiles)

Study Period Assessment, n (%)	CPX-351 First Tertile (N=52)	CPX-351 Second Tertile (N=53)	CPX-351 Third Tertile (N=51)	Control 7+3 (N=151)
Any TEAEs	52 (100)	53 (100)	51 (100)	151 (100)
TEAEs by Maximum NCI-CTC Grade				
Grade 1	1 (1.9)	0	0	2 (1.3)
Grade 2	6 (11.5)	3 (5.7)	1 (2.0)	12 (7.9)
Grade 3	26 (50.0)	32 (60.4)	33 (64.7)	92 (60.9)
Grade 4	10 (19.2)	8 (15.1)	9 (17.6)	16 (10.6)
Grade 5	9 (17.3)	10 (18.9)	8 (15.7)	29 (19.2)
Grade 3-5	45 (86.5)	50 (94.3)	50 (98.0)	137 (90.7)
TEAEs by Closest Relationship				
Not Related	3 (5.8)	1 (1.9)	0	8 (5.3)
Related	49 (94.2)	52 (98.1)	51 (100)	143 (94.7)
Serious TEAEs	24 (46.2)	32 (60.4)	30 (58.8)	65 (43.0)
TEAEs leading to disc.	1 (1.9)	1 (1.9)	0	2 (1.3)
TEAEs leading to death	9 (17.3)	10 (18.9)	8 (15.7)	29 (19.2)

Source: Exposure-response report Table 8.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

BSA-based dosing regimen was supported by the finding in the population PK analysis that BSA is a significant allometric factor on clearance and volume of distribution. Population PK analysis (n = 195) also showed that patient demographics such as body weight (range: 38.9 kg - 156.5 kg), body mass index (17.0 kg/m^2 - 48.1 kg/m^2), white blood cell count (0.2 x 10^9/L - 111 x 10^9/L), sex (61% male/39% female) and race (84.6% white/15.4% others) were not found to have a clinically meaningful influence on the PK parameters of total daunorubicin or cytarabine after adjusting dose by BSA. Refer to the pharmacometrics review in the Appendix 13.4.3 for more details. Safety and effectiveness of CPX-351 have not been established in pediatric patients and in pregnant or lactating women. The assessment of the effects of hepatic impairment, renal impairment and age on CPX-351 is further discussed in this section.

Hepatic Impairment: A dedicated hepatic impairment trial (CLTR0314-208) is currently ongoing. In population PK analyses, bilirubin was not found to be a significant covariate on PK parameters of daunorubicin or cytarabine. The exposure of daunorubicin and cytarabine were comparable (**Figure 7**) between patients across bilirubin categories: bilirubin < 1.2 mg/dL (n = 141), bilirubin ≥ 1.2 mg/dL to <1.8 mg/dL (n = 11) and bilirubin ≥ 1.8 mg/dL to ≤ 3.0 mg/dL (n = 5). In addition, despite a slightly increase in TEAEs leading to death for CPX-351 was observed in bilirubin category of ≥ 1.8 mg/dL to ≤ 3.0 mg/dL based on data from a small sample size (n = 11), there is generally no statistically significant difference in safety profiles across bilirubin categories and between CPX-351 and 7+3 treatment groups (**Table 7**). Therefore, no dosage adjustment is required for patients with a bilirubin level less than or equal to 3 mg/dL. No

studies were conducted and no further study will be planned in patients with bilirubin level greater than 3 mg/dL because intensive chemotherapy is not typically prescribed for patients with AML and moderate or severe hepatic impairment.

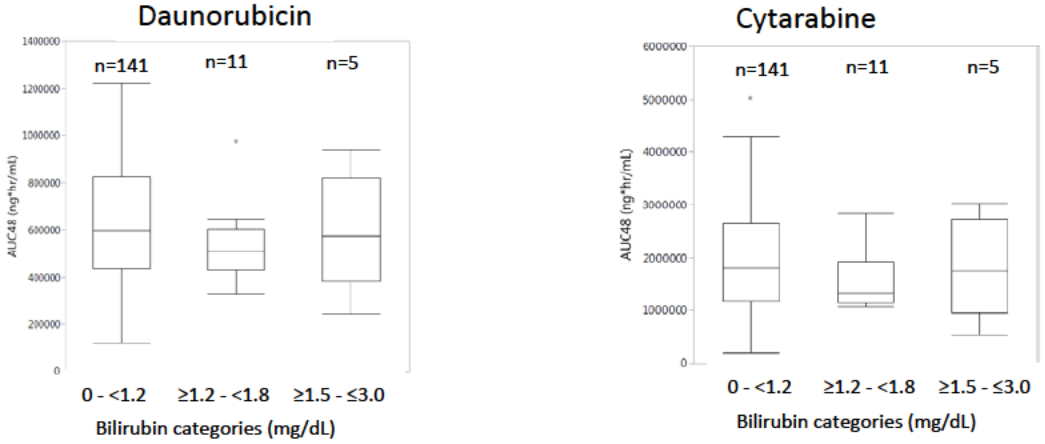


Figure 7: Comparison of AUC0-48h of total daunorubicin and cytarabine between different bilirubin categories in patients receiving CPX-351 44 mg/100 mg per m2 in Trial 301.

Source: Reviewers' analysis.

Table 7: Overall Summary of Treatment Emergent Adverse Events by Hepatic Function - Study Period (Pooled Safety Population).

	CPX-351			All Controls		
	BL Bilirubin <1.2 mg/dL N = 332	BL Bilirubin 1.2 – 1.8 mg/dL N = 32	BL Bilirubin 1.8 – 3.0 mg/dL N = 11	BL Bilirubin <1.2 mg/dL N = 216	BL Bilirubin 1.2 – 1.8 mg/dL N = 16	BL Bilirubin 1.8 – 3.0 mg/dL N = 4
Any TEAEs	332 (100)	32 (100)	11 (100)	216 (100)	16 (100)	4 (100)
TEAEs by Maximum NCI-CTC Grade	332 (100)	32 (100)	11 (100)	216 (100)	16 (100)	4 (100)
Grade 1	1 (0.3)	0 (0)	1 (9.1)	2 (0.9)	0 (0)	1 (25.0)
Grade 2	24 (7.2)	0 (0)	0 (0)	16 (8.4)	0 (0)	0 (0)
Grade 3	187 (56.3)	17 (81.3)	4 (36.4)	128 (58.6)	12 (75.0)	2 (50.0)
Grade 4	56 (16.9)	4 (12.5)	2 (18.2)	27 (12.6)	1 (6.3)	1 (25.0)
Grade 5	64 (19.3)	2 (6.3)	4 (36.4)	43 (19.5)	3 (18.9)	0 (0)
Grade 3 to 5	307 (92.5)	32 (100)	10 (90.9)	198 (90.7)	16 (100)	3 (75.0)
TEAEs by Closest Relationship						
Not related	11 (3.3)	1 (3.1)	0 (0)	15 (6.5)	1 (6.3)	0 (0)
Related	321 (96.7)	31 (96.9)	11 (100)	201 (93.5)	15 (93.8)	4 (100.0)
Serious TEAEs	193 (58.1)	18 (56.3)	7 (63.4)	101 (45.1)	5 (31.3)	1 (25.0)

	CPX-351			All Controls		
	BL Bilirubin <1.2 mg/dL N = 332	BL Bilirubin 1.2 – 1.8 mg/dL N = 32	BL Bilirubin 1.8 – 3.0 mg/dL N = 11	BL Bilirubin <1.2 mg/dL N = 216	BL Bilirubin 1.2 – 1.8 mg/dL N = 16	BL Bilirubin 1.8 – 3.0 mg/dL N = 4
TEAEs leading to discontinuation	7 (2.1)	1 (3.1)	0 (0)	3 (1.4)	0 (0)	0 (0)
TEAEs leading to death	64 (19.3)	2 (6.3)	4 (36.4)	43 (19.5)	3 (18.9)	0 (0)

Source: Reviewers' analysis.

Renal Impairment: A dedicated renal impairment trial has not been conducted. The PK population had 83 (42.6%) patients with a creatinine clearance (CL_{CR}) of 60 mL/min to 89 mL/min by Cockcroft Gault equation (C-G) (mild impairment) and 28 (14.4%) patients with a CL_{CR} of 30 mL/min to 59 mL/min (moderate impairment). The $AUC_{0\text{-}48h}$ apparently increased with the increasing in severity of renal function with the $AUC_{0\text{-}48h}$ of total daunorubicin and cytarabine about 40% higher in patients with moderate renal impairment compared to that in patients with normal renal function; however, the $AUC_{0\text{-}48h}$ was lower than that observed in 6 patients (2 of those with normal renal function, 3 with mild renal impairment and 1 with severe renal impairment) at an untolerated dose of 59 mg/134 mg per m^2 in Trial 101 (**Figure 8**).

Patients with mild (n = 139) and moderate (n = 54) renal impairment tended to have slightly higher Grade 3 to 5 TEAEs and serious TEAEs than patients with normal renal function (n = 181) in the CPX-351 treatment arm (**Table 8**). In addition, patients with moderate renal impairment (n = 54) in the CPX-351 treatment arm had higher Grade 3 to 5 TEAEs, serious TEAEs and TEAEs leading to death as compared to patients with moderate renal impairment (n = 29) in the control treatment arm. Patients with severe renal impairment were not enrolled in the registration trials. Based on the available PK and safety data, no dose adjustment is recommended for patients with mild or moderate renal impairment. A PMR will be required to evaluate the potential need of an alternative dosing regimen for patients with moderate and severe renal impairment in a future trial as VYXEOS is intended for patients with AML and impaired renal function in clinic.

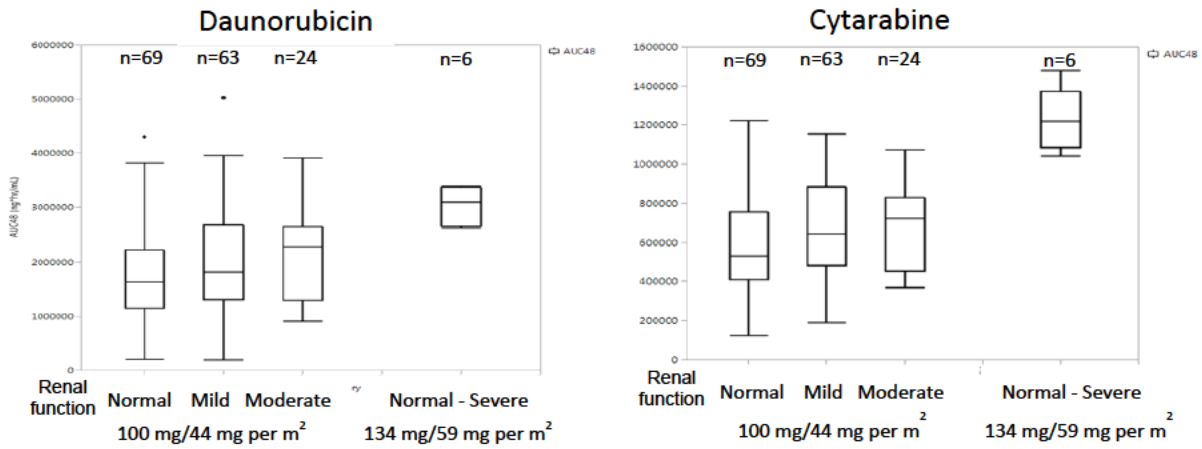


Figure 8: Comparison of $AUC_{0\text{-}48h}$ of Total Daunorubicin and Cytarabine between Different Renal Function Categories in Patients Receiving CPX-351 44 mg/100 mg per m^2 in Trial 301 and in 6 Patients (2 of Those with Normal Renal Function, 3 with Mild Renal Impairment and 1 with Severe Renal Impairment) Receiving an Untolerated Dose of 59 mg/134 mg per m^2 in Trial 101.

Source: Reviewers' analysis.

Table 8: Overall Summary of Treatment Emergent Adverse Events by Renal Function - Study Period (Pooled Safety Population)

	Number of subjects, n (%)					
	CPX-351			All Controls		
	Normal Renal Function N = 181	Mild Renal Impairment N = 139	Moderate Renal Impairment N = 54	Normal Renal Function N = 113	Mild Renal Impairment N = 94	Moderate Renal Impairment N = 29
Any TEAEs[a]	181 (100)	139 (100)	54 (100)	113 (100)	94 (100)	29 (100)
TEAEs by Maximum NCI-CTC Grade[b]	181 (100)	139 (100)	54 (100)	113 (100)	94 (100)	29 (100)
Grade 1	2 (1.1)	0	0	2 (1.8)	1 (1.1)	0
Grade 2	14 (7.7)	8 (5.8)	2 (3.7)	5 (4.4)	9 (9.6)	5 (17.2)
Grade 3	104 (57.5)	84 (60.4)	27 (50.0)	79 (69.9)	46 (48.9)	15 (51.7)
Grade 4	28 (15.5)	23 (16.5)	12 (22.2)	9 (8.0)	16 (17.0)	4 (13.8)
Grade 5	33 (18.2)	24 (17.3)	13 (24.1)	18 (15.9)	22 (23.4)	5 (17.2)
Grade 3 to 5	165 (91.2)	131 (94.2)	52 (96.3)	106 (93.8)	84 (89.4)	24 (82.8)
TEAEs by Closest Relationship[c]						
Not related	7 (3.9)	3 (2.2)	2 (3.7)	9 (8.0)	4 (4.3)	3 (10.3)
Related	174 (96.1)	136 (97.8)	52 (96.3)	104 (92.0)	90 (95.7)	26 (89.7)
Serious TEAEs	100 (55.2)	82 (59.0)	35 (64.8)	41 (36.3)	47 (50.0)	15 (51.7)
TEAEs leading to discontinuation	3 (1.7)	4 (2.9)	1 (1.9)	3 (2.7)	0	0
TEAEs leading to death	33 (18.2)	24 (17.3)	13 (24.1)	18 (15.9)	22 (23.4)	5 (17.2)

Source: Integrated Summary of Safety Table 45.

Age: Only elderly patients (60 to 75 years old) with newly diagnosed AML were enrolled in Trial 301; however, the Applicant proposes the use of CPX-351 in all adult patients. Based on the population PK analysis with limited data from a small sample size (n = 21) of patients aged less than 60 years old in all clinical trials, no significant association between age and dose-normalized $AUC_{0\text{-}48h}$ or C_{max} of total daunorubicin or cytarabine is observed (**Figure 9**). Thus, the inclusion of all adult patients in the indication statement is acceptable from a clinical pharmacology perspective.

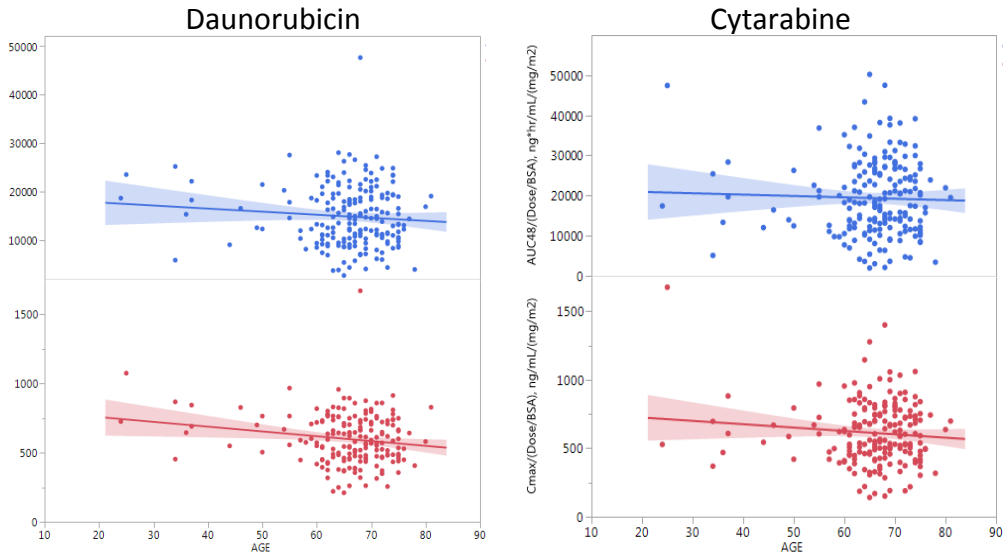


Figure 9: Associations of Patient Age with Dose-normalized AUC_{0-48h} (Blue) and C_{max} (Red) of Total Daunorubicin (Left Panels) and Cytarabine (Right Panels). Dots Represent Observations, while Lines and Colored-Areas represent Linear Regressions and 95% Confidence Intervals.
Source: Reviewers' analysis.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Drug-drug interaction studies have not been performed with CPX-351. The drug interactions with daunorubicin and cytarabine are expected to be the same for non-liposomal, liposomal and CPX-351 formulations. As CPX-351 contains the anthracycline daunorubicin, which has a known risk of cardiotoxicity and hepatotoxicity per literature and labeling, concomitant use of cardiotoxic or hepatotoxic agents may increase the risk of cardiotoxicity or hepatotoxicity. Cardiac or hepatic function should be monitored more frequently when VYXEOS is coadministered with cardiotoxic or hepatotoxic agents. Although the Applicant did not conduct any DDI trials in humans for CPX-351, drug interactions with inhibitors or inducers of CYP enzymes and common transporters are unlikely based on available clinical data and labeling for liposomal formulation of daunorubicin (DaunoXome®) and cytarabine (DepoCyt®) as well as non-liposomal formulation of daunorubicin and cytarabine.

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 9: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries
Pivotal Study				
CLTR0310-301	Phase 3, randomized, OL, active-controlled study of induction and consolidation with CPX-351 vs daunorubicin/cytarabine (7+3) Primary endpoint: OS	Up to 2 cycles of induction and 2 cycles of consolidation CPX-351: *Induction 1*: 100 units/m2, Days 1, 3 and 5 *Induction 2:*100 units/m2, Days 1 and 3 *Consolidation* :65 units/m2, Days 1 and 3 Daunorubicin/Cytarabine: *Induction 1:* 7+3 *Induction 2:* 5+2 *Consolidation:* 5+2	n=309 Age: 61-75 years Untreated AML of these subtypes: • t-AML • $_{MDS}$AML • $_{CMMoL}$AML • $_{de\ novo}$AML with MDS karyotype	US: 35 Canada: 4
Other Controlled Studies to Support Efficacy and Safety				
CLTR0308-204	Phase 2b OL, randomized, active-controlled study of induction and consolidation with CPX-351 vs daunorubicin/cytarabine (7+3) Primary endpoint: CR during the treatment phase	Up to 2 cycles of induction and 2 cycles of consolidation CPX-351: *Induction 1*: 100 units/m2, Days 1, 3 and 5 *Induction 2:* 100 units/m2, Days 1 and 3 *Consolidation* : 100 units/m2, Days 1 and 3 Daunorubicin/Cytarabine: *Induction 1:* 7+3 *Induction 2:* 5+2 *Consolidation:* Investigator's choice	n=126 Age: 60-75 Untreated AML	US: 17 Canada: 1
CLTR0308-205	Phase 2b OL, randomized, active-controlled study of induction and consolidation with CPX-351 vs Investigator's choice (intensive salvage) Primary endpoint: OS at 1 year	Up to 2 cycles of induction and 2 cycles of consolidation CPX-351: *Induction 1*: 100 units/m2, Days 1, 3 and 5 *Induction 2:* 100 units/m2, Days 1 and 3 *Consolidation* : 100 units/m2, Days 1 and 3 IC: *Induction 1:* ME based, 7+3, cytarabine+/- anthracycline +/- other *Induction 2:* IC *Consolidation:* IC	n=126 Age: 18-65 AML in first relapse	USA: 25 France: 4 Poland: 4 Canada: 2

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries
Uncontrolled Studies to Support Safety				

CLTR0305-101	Phase 1, OL, single arm dose escalation study
	
	Primary endpoint: MTD/RP2D determination
		Up to 2 cycles of induction and 1 cycle of consolidation
		
		CPX-351, IV, dose escalating cohorts:
		Cohort 1: 3 units/m2
		Cohort 2: 6 units/m2
		Cohort 3: 12 units/m2
		Cohort 4: 24 units/m2
		Cohort 5: 32 units/m2
		Cohort 6: 43 units/m2
		Cohort 7: 57 units/m2
		Cohort 8: 76 units/m2
		Cohort 9: 101 units/m2
		Cohort 10: 134 units/m2
			n=34
			
			Age ≥18
			
			AML:
			• ≥2nd relapse
			• First relapse
			  • DOR <6 mo
			  • Refractory to induction
			• Primary refractory
			ALL:
			• r/r T-cell, post nelarabine
			• other r/r
			
			MDS:
			• RAEB-2 with >10% blasts with ≥ 1 prior therapy (HMA)
				USA: 4

CLTR0310-206	Phase 2, OL, single arm PK study Primary endpoint: effect on cardiac repolarization following Induction 1 (QTcF)	Up to 2 cycles of induction and 2 cycles of consolidation	n=26 Age 18 -80 Newly diagnosed AML with adverse cytogenetics or secondary AML OR relapsed/refractory Aml ALL, or MDS,	US: 5

Source: FDA reviewers
Abbreviations: OL- open label; OS- overall survival; AML- acute myeloid leukemia; ALL- acute lymphocytic leukemia; MDS- myelodysplastic syndrome; t-AML- therapy-related AML; $_{MDS}$AML- AML with antecedent MDS; CMMoL- chronic myelomonocytic leukemia; $_{CMMoL}$AML- AML with antecedent CMMoL; RAEB- refractory anemia with excess blasts; QTcF- QT interval with Fridericia's correction; CR- complete response; MTD- maximum tolerated dose; RP2D- recommended phase 2 dose; HMA- hypomethylating agent; IC: investigator's choice; ME: mitoxantrone/etoposide; 7+3: standard induction regimen for AML consisting of cytarabine 100-200 mg/m2/day as a 7-day continuous infusion, and daunorubicin at 40-60 mg/m2/day on days 1, 2 and 3; 5+2: cytarabine 100 mg/m2/day as a 5-day continuous infusion, and daunorubicin 60 mg/ m^2 on days 1 and 2.
Note: For study 301, cytarabine 100 mg/ m^2 and daunorubicin 60 mg/ m^2 were used for 7+3 and 5+2; in 204, induction consisted of 40-65 mg/m2/day of daunorubicin during induction, based on investigator's choice.

7.1.2. Review Strategy

Data Sources

The key material used for this review of efficacy and safety includes:

- NDA 209401
- Relevant published literature
- Relevant information in the public domain

Study CLTR0310-301 (Study 301) was used for the primary efficacy analysis. Data from the remainder of the studies listed in Table 9 above were used for safety, and supportive data from 204 and 205 were used for efficacy as well, specifically to support an indication in the newly diagnosed population of patients, as well as a limitation to patients with the specified subgroups of AML (AML-MRC (b) (4) Safety data from Study 205 was used to expand the indication to all adult patients, rather than restrict the indication to the older population enrolled in Study 301.

Data sources include applicant study reports, protocol and amendments, SAP and amendments, data sets and literature referenced for study CLTR0310-301 and study CLTR0308-205.

Electronic data sets in the ADaM format and SAS programs were located at \\CDSESUB1\evsprod\NDA209401\0002\m5\datasets

Summaries of data and statistical analysis by the clinical reviewer were performed using JMP 12.0 and JMP Clinical 6.1 (SAS Institute, Inc., Cary,NC). MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD) was also used to look for safety signals. For the results of the primary efficacy analysis the methodologies used were SAS version 9.4.

Data and Analysis Quality

The quality and integrity of the submitted data were sufficient for the reviewers to review the application. See 7.4.3 for details regarding the adequacy of the submitted safety data.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

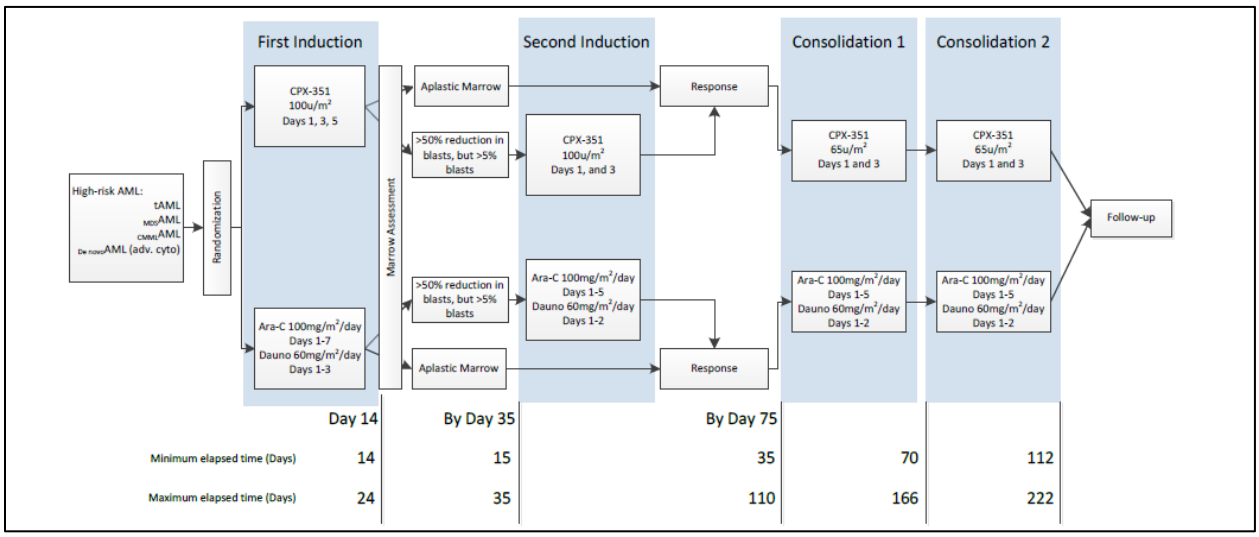
CLTR0310-301

Trial Design and Endpoints

The pivotal trial CLTR0310-301 titled "A 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" 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, $_{CMMoL}$AML and de novo AML with

karyotypic changes characteristics of myelodysplasia), per World Health Organization (WHO) 2008 criteria.

Figure 10: Study 301- Study Design



Source: Figure 1 Study Design, Applicant's Clinical Study Report for Study 301

Patients with ≥20% bone marrow (BM) or peripheral blasts were randomized (1:1) to receive either CPX-351 or standard induction treatment with cytarabine and daunorubicin (7+3 regimen) at the dose and schedule outlined in Figure 10. Randomization were stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL.

The study was designed in two phases. In the treatment phase, patients received up to two induction and two consolidation courses and are intensively monitored for safety (early deaths, adverse events, metabolic changes, etc.) and efficacy endpoints. Patient had a BM assessment on day 14 of induction 1; the protocol highly recommended a second induction of any documented reduction of leukemia burden and made it mandatory for patients with >50% reduction of blast BM percent on that assessment. This BM could be repeated if non-evaluable within 5-10 days for determination of need for second induction. Patients with aplasia or hyperplasia and <5% blasts would not receive second inductions. Patients who did not achieve a CR or CRi (see below) after 2 induction cycles were discontinued from study treatment. Patients who achieved a CR or CRi were eligible for up to 2 cycles of consolidation if they had adequate cardiac function (LVEF ≥50%) and ECOG PS of 0-2. Consolidation 1 was to be given between 35 and 75 days after the start of the last induction, and patients had to have adequate absolute neutrophil count (ANC) recovery (ANC>500/mcL) and platelet recovery (>50, 000/mcL). Consolidation 2 was to be given 35-56 days after the start of Consolidation 2.

Patients with ≥ 500 mg/m^2 prior cumulative anthracycline exposure could receive an alternate regimen of intermediate dose cytarabine at 1.5 g/ m^2 BID on days 1, 3 and 5, and those with <500 mg/ m^2 cumulative anthracycline exposure who had a >10% decrease in LVEF to <50% during the study could receive this alternate consolidation as well. Finally, patients in both arms could undergo allogeneic hematopoietic stem cell transplantation (HSCT) in lieu of or following consolidation. These patients continued to be followed for the primary endpoint.

The follow up phase 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).

Eligibility Criteria (summarized):

1. Age 60-75 years
2. AML per WHO 2008 criteria (>20% BM/peripheral blasts)
3. Documented antecedent hematologic disorder:
    - Therapy-related AML (t-AML)- documented prior cytotoxic/radiation therapy for an unrelated disease
    - $_{MDS}$AML: BM documentation of MDS prior to the AML diagnosis
    - $_{CMMoL}$AML: BM documentation of CMMoL prior to the AML diagnosis
    - $_{de\ novo}$AML: with fluorescence in-situ hybridization (FISH) or cytogenetic changes linked to MDS per WHO 2008 criteria
4. ECOG performance status (PS) 0-2
5. Adequate organ function:
    - creatinine <2 mg/dL
    - total bilirubin <2 mg/dL
    - AST/ALT <3xULN
    - LVEF ≥ 50% (echo or MUGA)
6. Patients were excluded if they had a history of a myeloproliferative neoplasm (MPN) with the exception of CMMoL, Acute promyelocytic leukemia (APML), had favorable cytogenetics (including t(8:21) or inv 16)or active CNS leukemia.
7. Patients could not have received prior therapy for AML, with the exception of hydroxyurea (HU) for control of WBC counts. They could have received therapy for MDS that ended at least 2 weeks prior to first dose of study drug, and toxicities for these drugs had to have recovered to ≤ grade 1 prior to initiation of therapy.
8. Patients could not have prior cumulative anthracycline exposure of >368 mg/ m^2 daunorubicin or equivalent.
9. Patients were excluded if they had any myocardial impairment that resulted in Class III or IV AHA heart failure could not be enrolled.
10. Patients could not have active or uncontrolled infection, hypersensitivity to cytarabine, daunorubicin or liposomal products, and could not have a history of Wilson's disease or other copper-metabolism disorders.

Study 301: Treatment

Treatment in each arm was per the following dose and schedule:

Figure 11: Study 301, Treatment Dose and Schedule

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 1and 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/m^2 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

Source: Applicant's CSR, Section 16.1.1, page 281 of Protocol CLTR0310-301, version 2.3

Patients received up to 2 cycles of induction and 2 cycles of consolidation, and were to be taken off treatment for:

- No response was achieved by day 56 after induction 2
- Progressive disease after initial response
- LVEF <50% before any treatment cycle
- Other unacceptable toxicity (undefined)

Consolidation could not be given until ANC recovered to >500/mcl and platelets to >50,000/mcl.

With regard to treatment interruptions, the protocol stipulated only that doses may be delayed due to toxicities (e.g. hypersensitivity reactions), and that any missed/delayed doses may be administered as soon as the patient recovered from that toxicity.

Concomitant Medications:

Patients could receive premedication with anti-emetics per institutional standards. Patients who developed hypersensitivity reactions were to be pre-medicated for subsequent infusions. Prophylactic anti-infectives was highly recommended for patients with ANC <500/mcL, per institutional protocol. Transfusion support was per institutional protocol. Growth factor use was per institutional protocol and according to ASCO criteria. Other anti-cancer treatment and other investigational agents were not permitted during the treatment phase.

Safety Assessments on Study 301 were per Figure 12:

Figure 12: Schedule of Assessments (from Protocol 301)

Each INDUCTION[1] 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			
Vital Signs		x									x				x			
ECOG Performance Status		x																
ECG		x															x	x
Registration & Randomization		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				x				x[9]		x	
PK sampling[7]			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													x[10]		x	x
Response Assessment															x[6]			
Cytogenetics/Molecular Studies		x	At the time of CR or CRi															
Adverse Events			Assess throughout Induction and Consolidation															
Concomitant Medications			Assess throughout Induction and Consolidation															
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]													

[1]The 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
[2]Second 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/m^2 cumulative daunorubicin-equivalent dose
[3]Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared
[4]Within 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
[5]Required 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
[6]Induction(s) only; see Section 8.4.1 for details on when response is assessed
[7]CPX-351 patients will be randomized to one of two PK sampling schedules: See Section 6.2 for the timing of PK draws
[8]Day 150 or 45 Days after the last treatment whichever is later
[9]After the last induction See Section 9.3
[10]See Section 9.3, Repeat ECHO/MUGA before the second consolidation if patient exceeds 500mg/m^2 of cumulative daunorubicin-equivalent dose

Study Endpoints:

The primary efficacy endpoint is overall survival (OS), which 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 were followed for up to 5 years.

The 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). CR and CRi were defined as follows:

Figure 13: Response Definitions, Study 301

Complete remission (CR)[3]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100,000/μL); independence from red cell transfusions
CR with incomplete recovery (CRi)[5]	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/μL]) **or** thrombocytopenia (<100 x 10^9/L [100,000/μL])

Source: Applicant's CSR, Section 16.1.1, page 287 of Protocol version 2.3

BM evaluations were required to confirm either CR or CRi. CRi could not be declared prior tday 35 to allow for adequate count recovery.

EFS was 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 were censored on the date they were last examined.

The induction treatment failure (ITF) is defined as failure to achieve a CR or CRi by the end of the induction period. The event date of induction treatment failure is derived using the field "Date Established" in the Disease Assessment CRF page during the induction period. Furthermore, for censoring of patients without events, the "date they were last examined" is the latest of the date of the last complete blood count (CBC) assessment or the date of the last disease assessment.

For response assessment, an independent hematopathologist evaluated the response assessment by reviewing bone marrow reports, data on peripheral blood ANC and platelet recovery, and transfusion reports. The response reported by the applicant in this study are those confirmed by the independent hematopathologist.

The clinical review team at FDA adjudicated the response assessment based on the submitted information. The analysis results based on the response assessment by the clinical review team at FDA will be discussed and compared with the results from the applicant in section 7.2.2.

In order to control the type I error rate at one-sided 0.025, a hierarchical testing procedure (Gatekeeping) would be implemented for testing the hypothesis in the order of primary endpoint (OS), secondary endpoint best response rate CR, secondary endpoint best response rate (CR + CRi)

Statistical Analysis Plan

Analysis Population

All primary efficacy analyses, except for the rate of stem cell transplant, were planned to be analyzed based on the intent to treat (ITT) population, which was defined as all patients who were randomized to the trial. Patients were assigned to treatment arm based on what they were randomized to receive.

The rate of stem cell transplant were planned to be analyzed based on the per protocol (PP) population, which was defined as all patients who have met inclusion/exclusion criteria and have received at least one dose.

Sample Size and Power Considerations

The study were planned to enroll 300 patients and assumed 10% drop out rate. With 236 deaths and assuming the median OS of 0.526 years in the control arm, this study has 93.7% power and a 1-sided significance level alpha of 0.025 to detect a hazard ratio of 0.635 in OS. Patients would be followed until the last patient enrolled had been followed for ≥ 1.2 years.

Assuming the response rate in the control arm is 42%, the study also provided 99.99% power and a one-sided significance level alpha of 0.025 to detect an absolute improvement of 32% in the response rate (CR + CRi) in the CPX-351 arm.

The study also provided >99.9% power and 1-sided significance level alpha of 0.025 to detect a hazard ratio of 0.35 in EFS between two arms.

Analysis Method

The primary efficacy endpoint OS were planned to be analyzed by the log-rank test stratified by the randomization stratification factors. The distribution of OS in each arm were planned to be estimated using the method of Kaplan-Meier by treatment group. The hazard ratio were planned to be analyzed by the Cox proportional hazard model.

Response rate (CR, CR + CRi), complete response rate (CR, CRi), rate of transfer for stem cell transplant would be analyzed using the Mantel-Haenszel test stratified by the randomization stratification factors.

The rate of stem cell transplant would 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.

Remission duration and EFS would be analyzed by stratified log rank test. The hazard ratio were planned to be analyzed by the Cox proportional hazard model.

Sensitivity Analysis of OS

A sensitivity analysis was planned by the applicant to assess the potential bias due to transplant on OS and on the analyses would to be performed by comparing OS in the two arms with patient censored at the time of transplant Stratified by the randomization stratification factors The applicant considered that this analysis would account for the impact of transplant on survival.

Sensitivity Analysis of EFS

The reviewer requested that the applicant re-define EFS based on the following alternative definition, and the results will be discussed in the section of 7.2.2:

Define induction treatment failure (ITF) as no CR or CRi in induction and use the date of death as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR or CRi, or death from any cause, whichever comes first. Note that this method uses date of death as the event date for ITF. Earlier dates with marrow examinations showing no CR or CRi are not used to set the event date for ITF. Patients with induction treatment failure still alive at the time of analysis should be censored at the date of last assessment just as for patients who are surviving in CR or CRi.

Interim Analysis

An analysis of induction response (CR + CRi) would be performed after all patients have been accrued and completed induction and consolidation treatment. This response analysis would 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 study would not stop after this analysis. No alpha was allocated for this interim analysis.

Protocol Amendments

Summary of Changes Related to Statistical Evaluation of Efficacy in Version 2.0, dated March 12, 2013

- Increase the sample size from 240 in the original version of the protocol to 300. This sample size calculation was based on the assumption of median OS of 0.526 year in the control arm and hazard ratio of 0.635. The analysis of the OS will be performed after 236 deaths have occurred. This sample size provided 94% power and 1-sided 0.025 significance level.

  For the secondary endpoint of EFS, this sample size will provide >99.9% power and 1-sided significance level alpha of 0.025 to detect a hazard ratio of 0.35 and median EFS of 42 days in the control arm.

  For the secondary endpoint of RR, the sample size will provide 99.99% power and 1-sided significance level alpha of 0.025 to detect an absolute improvement of 32% in the CPX arm assuming the RR is 42% in the control arm.

Summary of Changes Related to Statistical Evaluation of Efficacy in Version 2.2, dated October 9, 2013 and in Version 2.3, dated November 4, 2013.

- The changes in version 2.2 and 2.3 of the protocol are mainly administrative amendment.

Summary of Other Relevant Major Protocol Amendments:
Version 2.0:

- Additional of optional consolidation schedule for patients with >500 mg/ m^2 prior cumulative anthracycline exposure
- Increased PK and copper sampling

Version 2.2:

- Removal of exception to SAE reporting for hospitalizations due to uncomplicated febrile neutropenia, grade 1-3 bleeding events (with or without platelet transfusions) and hospitalizations due to disease progression. These were not included in SAE reporting prior to this amendment (see 7.4.3 for more details on the impact of this assessment on the safety analysis).

7.2.2. Study Results

Compliance with Good Clinical Practices

The applicant stated in M2.5, section 1.7, that the CPX-351 development program has been carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki (2008), and standard operating procedures for clinical research and development at Celator Pharmaceuticals (a Jazz Pharmaceuticals company).

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in the appendix (0). The applicant submitted financial disclosure information from all of the investigators and subinvestigators from Studies 204, 205, 206 and 301. No financial interests or arrangements were reported for any of the investigators or subinvestigators.

Patient Disposition

Of the 458 patients screened, 309 patients were randomized in Study 301: 153 to the CPX-351 arm and 156 to the control arm; these were the patients who comprised the ITT population in the study for the primary efficacy analysis. Four patients in the control arm withdrew consent before initiation of therapy, and a second received idarubicin instead of daunorubicin therapy, which constituted a protocol violation, such that only 151 patients in the control arm received control therapy.

The applicant submitted the following disposition analysis for patients on Study 301:

Table 10: Applicant Assessed ITT Patient Disposition, Study 301

	CPX-351 N=153 n (%)	7+3 N=156 n (%)	Total N=309 n (%)
Completion of treatment	22 (14)	10 (6.4)	32 (10)
Persistent disease: lack of response to treatment	49 (32)	70 (45)	119 (39)
Relapsed disease: reappearance of disease	4 (2.6)	5 (3.2)	9 (2.9)
Patient will receive a stem cell transplant	37 (24)	21 (13)	58 (19)
Unacceptable toxicity	4 (2.6)	2 (1.3)	6 (1.9)
Patient non-compliance with protocol	0	0	0
Administration of non-protocol chemotherapy	2 (1.3)	7 (4.5)	9 (2.9)
Intercurrent illness	5 (3.3)	4 (2.6)	9 (2.9)
Discretion of investigator	6 (3.9)	6 (3.8)	12 (3.9)
Consent withdrawn	3 (2.0)	9 (5.8)	12 (3.9)
Lost to follow-up	0	0	0
Death	12 (7.8)	17 (11)	29 (9.4)
Other	9 (5.9)	5 (3.2)	14 (4.5)

Source: Applicant's Clinical Study Report, Table 14.1.6

Disposition for the ITT population as adjudicated by FDA is depicted in Table 11 below.

The date of the database lock was 12/31/2015. There were 131 patients (85.6%) withdrew from the treatment in the CPX-351 arm vs. 146 patients (93.6%) in the 7+3 arm.

In the per protocol population, 29 subjects (8 in the CPX-351 arm and 21 in the 7+3 arm) were excluded: 24 subjects for failing 1 or more inclusion or exclusion criteria (8 in the CPX-351 arm and 16 in the 7+3 arm), 4 subjects for not receiving at least 1 dose of assigned study drug (0 in the CPX-351 arm and 4 in the 7+3 arm), and 1 for both reasons (in the 7+3 arm)

Table 11: FDA Adjudicated Patient Disposition, Study 301

		CPX-351 (N=153)	7+3 (N=156)	Total (N=309)
Patients randomized (ITT)		153 (100%)	156 (100%)	309 (100.0%)
Treated		153 (100%)	151 (97%)	304 (98%)
Completed treatment		23 (15%)	11 (7%)	34 (11%)
CR		21 (14%)	11[a] (7%)	32 (10%)
CRi		2 (1%)	-	2 (0.7%)
Discontinued early		130 (85%)	140 (90%)	270 (87%)
Reason for early d/c				
Lack of efficacy		46 (30%)	76 (50%)	122 (39%)
HSCT*		37[b] (24%)	20[c] (13%)	57 (18%)
	CR/CRi	31 (20%)	18 (12%)	49 (16%)
	other	6 (4%)	2 (1%)	8(3%)
AE		28 (18%)	20 (13%)	48 (16%)
Death		12 (8%)	16 (10%)	28 (9%)
	No /decreasing blasts	9 (6%)	9 (6%)	18 (6%)
Physician decision		5 (3%)	4 (3%)	9 (3%)
Consent withdrawal		1 (0.7%)	3 (2%)	4 (1%)
Unknown		1 (0.7%)	1 (0.7%)	2 (0.7%)
Per protocol population		145 (94.8%)	135 (86.5%)	280 (90.6%)
Safety population		153 (100%)	151 (96.8%)	304 (98.4%)

Source: FDA reviewer analysis
[a]Two patients on the control arm who achieved CR did not have any documented BM or PB blasts. [b]Of these 37 patients for whom treatment was discontinued in order to go to HSCT, 1 relapsed before actually undergoing HSCT, a second got a consolidation cycle with cytarabine (after 1 cycle each of induction and consolidation with CPX-351) and 1 received conditioning followed by "leukocyte infusion" on the CRF, with no further details provided. [c]2 patients relapsed after treatment discontinuation for HSCT and never underwent transplant; a 3rd patient for whom HSCT was given as reason for discontinuation, and who was in remission, got decitabine and only went to HSCT 120 days after treatment discontinuation. [x]Listed here are only patients for whom HSCT was given as the reason for treatment discontinuation. Patients who completed treatment and then went to HSCT, or who relapsed and then went to HSCT, are not included in these numbers.

On the CPX-351 arm, 13 of the 28 patients for whom treatment was discontinued due to AE were in CR (n=8) or CRi (5); on the control arm 11 of the 20 patients for whom AE was the reason for treatment discontinuation were in CR (n=3) or CRi (n=7).

Reviewer Comment: It is noted that in some instances where patient disposition (with regard to the reason for treatment discontinuation) was recorded on the eCRF as progressive disease or lack of efficacy, this was done in the context of a patient who achieved >50% decrease in BM blast count on their day 14-21 day BM assessments (with at least 10% cellularity) and thus would technically have been eligible for induction 2 as early as day 14 of induction 1. In these cases where the verbatim term given for discontinuation was toxicity, this was reflected as such, but in those where there was no reported toxicity and the ADAE dataset did not reflect any notable grade 3 or severe toxicities, this was recoded by the FDA as "physician decision." In any case, due to 6 clinical scenarios in which this was the case, it is possible that the number of patients for whom treatment was truly ineffective may have been overestimated, as the outcome had they received a second dose of induction is unknown and unpredictable. Since this was the approach used in both arms (3 subjects per arm), this does not appear to affect the overall risk:benefit assessment, but the disposition terms in Table 11 must be interpreted with this in mind.

Further, there were patients for whom both the coded and verbatim terms for reasons for discontinuation of therapy were progressive disease/lack of efficacy, but for whom the BM assessments before treatment discontinuation had <5% blasts during induction, with associated persistent grade 4 neutropenia and/or thrombocytopenia (day 42 or beyond) at the time of discontinuation (CRh). When this was the case, reason for discontinuation was thought to be reflected more accurately as toxicity (persistent cytopenia), rather than true lack of efficacy. These patients with CRh were not considered to have achieved a CRi per the FDA analysis, according to which the term CRi was reserved for patients who had a maximum of grade 3 thrombocytopenia or neutropenia associated with <5% BM blasts, or for those who had persistent thrombocytopenia or neutropenia which was rising and then immediately received their next course (consolidation 1, e.g. USUBJID (b) (6)).

Finally, the 2 patients on the control arm who achieved CR but did not have any blasts at screening does not significantly affect interpretation of the study results, as these would favor the control arm, and make it more difficult for CPX-351 to have an effect when compared to the control arm.

Protocol Violations/Deviations

The applicant reported that 9 subjects (4 patients [2.6%] in the CPX-351 arm vs. 5 [3.2%] in the 7+3 arm) had a major protocol deviation. On the CPX-351 arm, this included 2 subjects with a 1 week delay after randomization before receiving the study drug, 1 delayed SAE reporting for a subject who died, and 1 subject who received 100 units/ m^2 instead of 65 units/m^2 during consolidation. In the control arm, 2 major violations were assignment of the wrong AML type, 1

included the patient who got idarubicin instead of daunorubicin, 1 subject had a delay in receiving daunorubicin, and 1 subject did not sign the informed consent form for Amendment 2 of the protocol.

The remainder of the protocol violations was not categorized as major, and they included violation of the eligibility criteria. In the CPX-351 arm, 9 patients with these violations included: a misdiagnosis or no confirmation of the AML subtype following screening (n=2), laboratory values outside of the acceptable range (n=1), lack of documentation of ≥20% blasts in the blood or BM (n=1), administration of therapy for MDS given within 2 weeks of study treatment (n=3), patient enrolled with history of MPN other than CMMoL (n=1) and prior treatment intended for induction therapy of AML given before initiation of therapy (n=1). On the control arm, violations of eligibility criteria occurred in 17 patients (1 patient had 2 violations), which included: laboratory values outside of the acceptable range (n=2), lack of documentation of ≥20% blasts in the blood or BM (n=3), administration of therapy for MDS given within 2 weeks of study treatment (n=6), prior treatment intended for induction therapy of AML given before initiation of therapy (n=4), prior cumulative anthracycline exposure of >368 mg/ m^2 (n=2) and active or uncontrolled infection (n=1).

Reviewer comment: Overall, the protocol violations described are not expected to significantly impede interpretation of the study results.

Demographic Characteristics

Demographic information for the patients on Study 301 are summarized in Table 12. The median age was 68 years in both treatment arms. The majority of the patients were males (61.4% in the CPX-351 arm and 61.5% in the 7+3 arm), white (83.7% in the CPX-351 arm and 89.1% in the 7+3 arm) and treated in the United States (94.1% in the CPX-351 arm and 94.2% in the 7+3 arm).

Table 12: Demographic Characteristics, ITT population, Study 301

	CPX-351 (N = 153) n (%)	**7 + 3** (N = 156) n (%)	**Total** (N = 309) n (%)
Sex			
Male	94 (61.4)	96 (61.5)	190 (61.5)
Female	59 (38.6)	60 (38.5)	119 (38.5)
Age			
Mean years (SD)	67.8 (4.2)	67.7 (4.1)	67.7 (4.1)
Median (years)	68.0	68.0	68.0
Min, max (years)	60, 75	60, 75	60, 75
Age Group			
< 65 years	39 (25.5)	41 (26.3)	80 (25.9)

	CPX-351 (N = 153) n (%)	7 + 3 (N = 156) n (%)	Total (N = 309) n (%)
≥ 65 years	114 (74.5)	115 (73.7)	229 (74.1)
60-64 years	39 (26)	41 (26)	80 (26)
65-69 years	57 (37)	61 (39)	118 (38)
70-75 years	57 (37)	54 (35)	91 (29)
ECOG PS			
0	37 (24)	45 (29)	82 (27)
1	101 (66)	89 (57)	190 (61)
2	15 (10)	22 (14)	37 (12)
Race			
White	128 (83.7)	139 (89.1)	267 (86.4)
Black or African American	7 (4.6)	6 (3.9)	13 (4.2)
Asian	6 (3.9)	2 (1.3)	8 (2.6)
American Indian or Alaska Native	1 (0.7)	0	1 (0.3)
Multiple	0	1 (0.6)	1 (0.3)
Other	11 (7.2)	8 (5.1)	19 (6.2)
Ethnicity			
Hispanic or Latino	7 (4.6)	7 (4.5)	14 (4.5)
Not Hispanic or Latino	146 (95.4)	149 (95.5)	295 (95.5)
Region			
United States	144 (94.1)	147 (94.2)	291 (94.2)
Canada	9 (5.9)	9 (5.8)	18 (5.8)

Source: FDA reviewer analysis

Table 13: Stratification Factors, ITT population, Study 301

	CPX-351 (N = 153) n (%)	7 + 3 (N = 156) n (%)	Total (N = 309) n (%)
Age Category			
60 – 69 years	96 (62.8)	102 (65.4)	198 (64.1)
70 – 75 years	57 (37.3)	54 (34.6)	111 (35.9)
AML Type			
$_{CMMoL}$ AML	11 (7.2)	12 (7.7)	23 (7.4)
De novo AML with MDS karyotype	41 (26.8)	37 (23.7)	78 (25.2)
$_{MDS}$ AML *with* prior HMA treatment	50 (32.7)	55 (35.3)	105 (34.0)
$_{MDS}$AML *without* prior HMA treatment	21 (13.7)	19 (12.2)	40 (12.9)
Therapy related AML (t-AML)	30 (19.6)	33 (21.2)	63 (20.4)

Source: FDA reviewer analysis

There were 25 patients (8.1%) on study with NPM1 mutations (13 [8.5%] in the CPX-351 arm and 12 [7.7%] in the 7+3 arm), 43 patients (13.9%) with FLT3 mutations (22 [14.4%] in the CPX-351 arm and 21 [13.5%] in the 7+3 arm) and 17 patients (5.5%) with CEBPA (12 [7.8%] in the CPX-351 arm and 5 [3.2%] in the 7+3 arm).

Table 14: Cytogenetics and Specific Mutations, ITT, Study 301

	CPX-351 N = 153 n (%)	7 + 3 N = 156 n (%)	Total N = 309 n (%)
Cytogenetic risk group[a]			
Adverse/poor	73 (48)	83 (53)	156 (50)
Unknown	8 (5)	10 (6)	18 (6)
NPM1			
Positive	13 (8.5)	12 (7.7)	25 (8.1)
Negative	126 (82.4)	132 (84.6)	258 (83.5)
Missing	14 (9.2)	12 (7.7)	26 (8.4)
FLT3			
Positive	22 (14.4)	21 (13.5)	43 (13.9)
Negative	115 (75.2)	118 (75.6)	233 (75.4)
Missing	16 (10.5)	17 (10.9)	33 (10.7)
CEBPA			
Positive	12 (7.8)	5 (3.2)	17 (5.5)
Negative	123 (80.4)	131 (84.0)	254 (82.2)
Missing	18 (11.8)	20 (12.8)	38 (12.3)

Source: FDA reviewer analysis
[a]Per NCCN guidelines version 2.2014

Reviewer comment: There was a slightly higher percentage of patients in the control arm with adverse cytogenetics and a slightly higher incidence of CEBPA mutations in the CPX-351 arm, but overall, the degrees of difference are not expected to have a major impact on the study results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

CPX-351 and 7+3 therapy were given by the healthcare staff such that compliance was not of concern. Overall, 100% of patients on the CPX-351 and 97% of patients on the control arm received at least one cycle of induction. Thirty one percent of patients on the CPX-351 arm and 34% on the control arm received a second cycle of induction. More patients on the CPX-351 arm received consolidation overall (32% received at least 1 cycle) compared to the control arm (21%), and this was true for a second consolidation cycle as well (15% on the CPX-351 arm and 7% on the control arm. See section 7.4.2 for a more detailed analysis of treatment exposure.

Use of growth factors and antibiotics:

Protocol 301 "highly recommended" the use of prophylactic antibiotics in until ANCs returned to 500/uL or greater (Protocol CLTR0310-301, Section 7.4.2), and the choice of anti-infectives was left to institutional standards. Overall, all but 3 patients on study received an anti-infective at some point during the treatment period: 151 patients on the CPX-351 arm (99%) and 150 patients on the control arm (99%).

Protocol 301 advised the use of growth factors according to ASCO criteria and institutional protocol. Overall, 49 patients on the CPX-351 arm (32%) received at least one growth factor during the treatment period, compared to 40 patients on the control arm (26%). This is consistent with the prolonged neutropenia seen with CPX-351 therapy (see section 7.4.4 for details) .This was predominantly granulocyte colony stimulating factor (GCSF), although 6 patients on the CPX-351 arm received GMCSF and 6 patients received pegylated-GCSF.

Reviewer comment: The administration of growth factors and antibiotics are part of practice of medicine that should be described in the PI but not included in the dosage and administration section.

Efficacy Results – Primary Endpoint

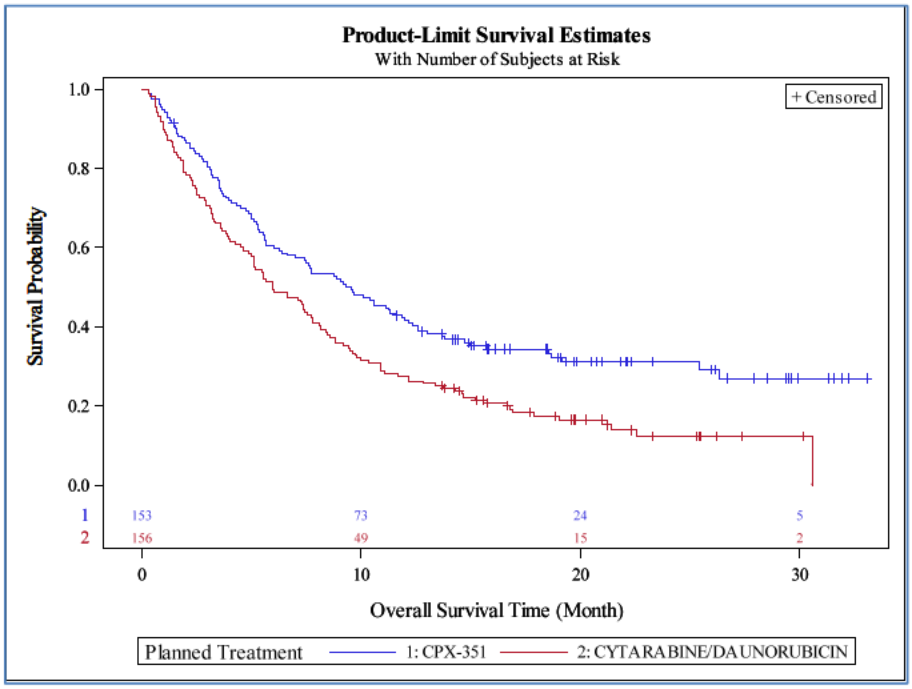
The efficacy analysis results on overall survival are shown in the table below. The median survival time was 9.6 months for the CPX-351 arm and 5.9 months for the control arm. The hazard ratio was 0.69 with 95% CI of [0.52, 0.90]. The 2-sided p-value from the stratified log-rank test was 0.005 and was statistical significant.

Table 15: Primary Analysis of Overall Survival, ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)
Events, n (%)	104 (68.0)	132 (84.6)
Censored, n (%)	49 (32.0)	24 (15.4)
Median time, months (95% CI)	9.6 (6.6, 11.9)	5.9 (5.0, 7.8)
HR (95% CI) [a]	0.69 (0.52, 0.90)	
2-sided p-value [b]	0.005	

Source: FDA reviewer analysis
[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML subtype (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).
[b] The 2-sided p-value is based on a stratified log-rank test with the same stratification factors as the above Cox proportional hazards model.

Figure 14: Kaplan-Meier Curve of Overall Survival, ITT, Study 301



Source: FDA reviewer analysis

Reviewer comment: The performance of the control arm was consistent with, perhaps even slightly better than, the poor results expected with 7+3 treatment in this population. According to the SEER database, 1-year OS for patients with AML aged 65-74 is about 30%; the subpopulation of t-AML and AML-MRC included in this trial are expected to have a prognosis that is worse than the overall AML population, and the HR on Study 301 reveals a survival benefit over the expected prognosis in this population.

Sensitivity Analysis

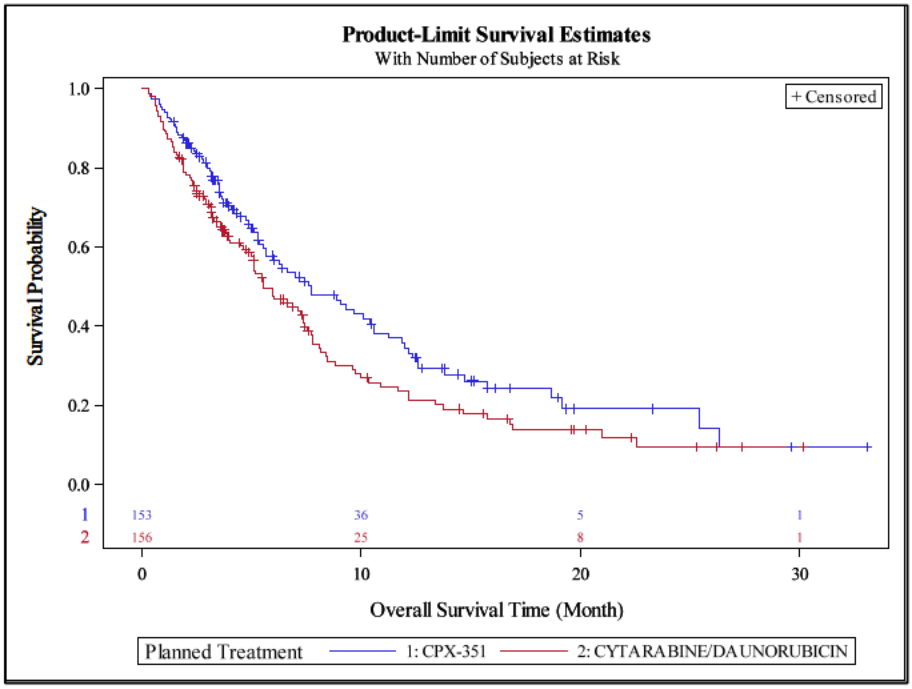
Sensitivity analysis of overall survival on the impact of HSCT was performed by censoring the OS of the patients who went through HSCT at the time of HSCT. The analysis results are shown in the table below. Subjects in the CPX-351 treatment group had a lager median survival time compared with those in the control group.

Table 16: Sensitivity Analysis of Overall Survival, ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)
Events, n (%)	86 (56.2)	106 (68.0)
Censored, n (%)	67 (43.8)	50 (32.1)
Median time, months (95% CI)	7.8 (5.7, 10.4)	5.6 (4.9, 7.4)
HR (95% CI) [a]	0.81 (0.60, 1.09)	
2-sided p-value [b]	0.16	

Source: FDA reviewer analysis
[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).
[b] The 2-sided p-value is based on a stratified log-rank test with the same stratification factors as the above Cox proportional hazards model.

Figure 15: Kaplan Meier Curve of Overall Survival



Source: FDA reviewer analysis

Reviewer Comment

- General survival analysis assumes non-informative censoring that time to censoring and time to event are independent conditional on the covariates. In this sensitivity analysis, this assumption implies that the survival distribution for the patients who had transplant is the same as those who did not have transplant, which is unlikely to be true, as in general transplant may prolong survival. Therefore, the estimate of treatment effect may still be a biased estimate in this sensitivity analysis.

- There were 52 patients (34%) went through stem cell transplant in the CPX-351 arm, while 39 patients (25%) went through stem cell transplant in the 7+3 arm. By censoring more patients on the control arm than the CPX-351 arm, the bias may be in favor of the control arm.

Of the 52 patients on the CPX-351 arm who went to HSCT after CPX-351 treatment, 31 (20%)

had achieved a CR with CPX-351 treatment, and an additional 6 (4%) had achieved a CRi. This included 34 patients for whom treatment was discontinued in CR or CRi to go to HSCT; one of these patients (CRi) relapsed in the interim between treatment and HSCT. In sum, 31 patients on the CPX-351 arm (20%) had HSCT in first CR, and an additional 6 (4%) were transplanted in first CRi, for a total of 37 (24%) transplanted in first CR/CRi. On the control arm, 20 (13%) of the 39 patients who ultimately proceeded to transplant had achieved a CR, and an additional 3 (2%) achieved a CRi; this included 18 patients for whom reason for treatment continuation was HSCT. None of these 18 patients had a subsequent relapse prior to HSCT. Nineteen patients on the control arm (12%) were transplanted in first CR, and additional 4 patients (3%) were transplanted in first CRi, for a total of 23 (15%) patients transplanted in first CR/CRI.

Reviewer comment: Although the results of this sensitivity analysis censoring patients at HSCT show no statistically significant difference between the arms, it is noted that a) the trend towards increased survival in the CPX-351 arm is maintained and b) the limitations noted above, namely that approximately 10% more patients on the CPX-351 arm proceeded to HSCT than on the control arm, 23 in CR or CRi, are relevant. Patients who do not achieve remission are unlikely to proceed to HSCT, and transplant outcomes in general appear to be improved in patients with a lower disease burden going into HSCT, although this has been challenged recently in certain patient population not relevant to this review (Schetelig 2015), such that CPX-351 treatment allowed more patients to proceed to potentially curative therapy. Finally, the applicant's landmark analysis of survival in patients who proceeded to HSCT after CPX-351 or control therapy, in which patients in the CPX-351 arm had lower 100-day non-relapse mortality than the control arm, and median survival patients was improved compared with those in the control arm (median survival NR in the CPX-351 arm vs 10.25 months in the control arm, HR 0.46 (95% CI 0.24, 0.89, CSR Table 14.2.1.5)), although necessarily exploratory in nature, further supports the notion that CPX-351 therapy prior to HSCT does not increase the risk of transplant related mortality (TRM) after HSCT, which is sometimes the case with therapies for AML and further supports a favorable benefit:risk assessment.

Efficacy Results – Secondary and other relevant endpoints

Best Response Rate (CR, CR+CRi) – Based on Applicant Adjudicated Response Assessment

The best response rates were summarized in the table below. A significantly greater proportion of subjects achieved CR in the CPX-351 arm compared with the control arm (37.3% vs. 25.6%, 2-sided p-value = 0.040). Similarly, a significantly greater proportion of subjects achieved CR + CRi in the CPX-351 arm compared with the control arm (47.7% vs. 33.3%, 2-sided p-value = 0.016).

Table 17: Best Response Rate (Applicant Adjudication), ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)	2-sided p-value
CR	57 (37.3%)	40 (25.6%)	0.040
CR + CRi	73 (47.7%)	52 (33.3%)	0.016

Source: FDA reviewer analysis

Best Response Rate (CR, CR+CRi) – Based on FDA Adjudicated Response Assessment

The clinical review team adjudicated the response assessment based on the applicant submitted information. Table 18 below summarizes the discrepancies between the FDA and applicant assessed CR/CRi rates in Study 301. Upon FDA review of the notes made by the independent hematopathologist when assessing responses in Trial 301, it was noted that in many cases, information from subsequent BM or CBC assessments were used to determine response. For example, in the case of USUBJID (b) (6), the patient had a BM that showed 1% blasts by morphology in a marrow with 10% cellularity on 6.6.13, which was induction 2 day 35. CBC on that date showed incomplete recovery of counts, with an ANC above 2000 and a platelet count of 21,000/mcL, and rose to 70,000/mcL on day 42. The applicant assessed this patient as a nonresponder, and FDA adjudicated this to be a CRi.

Table 18: Trial 301: FDA Adjudication of Applicants Best Response Assessment, Study 301

Treatment Arm	Subject ID	FDA Response Assessment	Applicant Response Assessment
CPX-351	(b) (6)	CR	CRi
		CR	CRi
		CR	CRi
		CRi	No response
		CRi	No response
		CRi	No response
		No response	CR
		No response	CR
7+3		CR	CRi
		CR	No response
		CRi	No response
		CRi	No response
		No response	CR
		No response	CRi
		No response	CRi

Source: FDA reviewer analysis

Reviewer comment: Upon initial review, there were three other patients ((b) (6) on the CPX-351 arm and (b) (6) and (b) (6) on the control arm) for whom response assessment was discrepant between the applicant and FDA. In response to an IR containing all of the discrepancies, the applicant stated that upon their review of the re-adjudicated cases, they agreed with FDA adjudication of all of the patients included above. They presented their reasons for disagreement for the other 3 patients, and upon review, FDA agreed with the applicant's assessment for these 3 patients.

Table 19 summarized the analysis results based on FDA adjudicated response assessment. For

this analysis, a significantly greater proportion of subjects achieved CR in the CPX-351 arm compared with the control arm (37.9% vs. 26.3%, 2-sided p-value = 0.036), although the rates were slightly different than those assessed by the applicant.

Table 19: Best Response Rate (FDA Adjudication), ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)	2-sided p-value
CR	58 (37.9%)	41 (26.3%)	0.036
CR + CRi	74 (48.4%)	52 (33.3%)	0.012

Source: FDA reviewer analysis

Reviewer Comment:

Durable CR is the endpoint established as reasonably likely to predict clinical benefit for patients with acute leukemia (Appelbaum 2007). The predictive value of CRi is uncertain. The applicant did not collect MRD across their development program, so there is no supportive data for the CRis. The discrepancies noted above between the applicant's and FDA analyses do not translate into significantly different CR rates, and the difference between the arms remains statistically significant; the CR rate in the label should reflect those assessed by FDA. Also, overall, given the OS benefit in the CPX-351 arm, the CR rates serve only as supportive evidence for efficacy and the discrepancies do not impact this endpoint, which is the basis of the approval recommendation.

Remission Duration

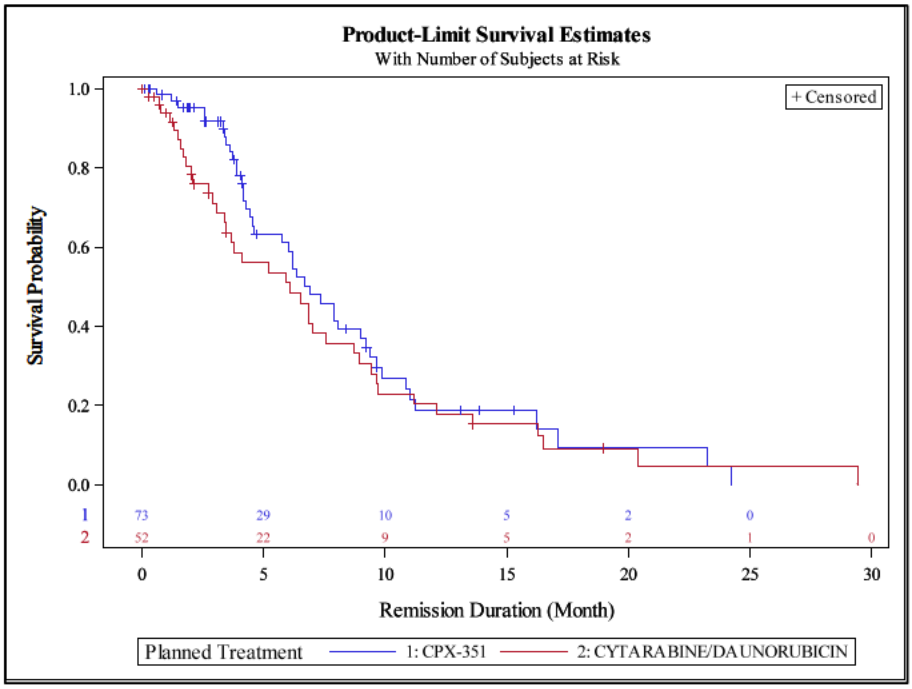
For patients who achieve CR/CRi, the median follow up time was 4.1 month in the CPX-351 arm vs. 3.4 months in the control arm. Median of remission duration was 6.9 months in the CPX-351 arm vs. 6.1 months in the control arm. The hazard ratio is 0.77 (95% CI [0.47, 1.26]).

Table 20: Remission Duration, Study 301

	CPX-351 (N = 73)	Control (N = 52)
Events, n (%)	31 (42.5)	13 (25.0)
Censored, n (%)	42 (57.5)	39 (75.0)
Median time, months (95% CI)	6.9 (4.6, 9.2)	6.1 (3.4, 8.7)
Range, months	(0.03, 24.2)	(0.03, 29.4)
HR (95% CI) [a]	0.77 (0.47, 1.26)	

Source: FDA reviewer analysis
[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).

Figure 16: Kaplan Meier Curve of Remission Duration



Source: FDA reviewer analysis

Reviewer's Comments:

The comparison of the duration of remission was based on responders only (i.e. patients who achieved CR/CRi), which is not an ITT population.

Event-Free Survival – Primary Analysis

The event free survival was statistically significantly longer for patients in the CPX-351 arm than patients in the control arm (2-sided p value = 0.02). The median EFS was 2.5 months in the CPX arm vs 1.3 months in the control arm. The hazard ratio is 0.74 (95% CI = [0.58, 0.96])

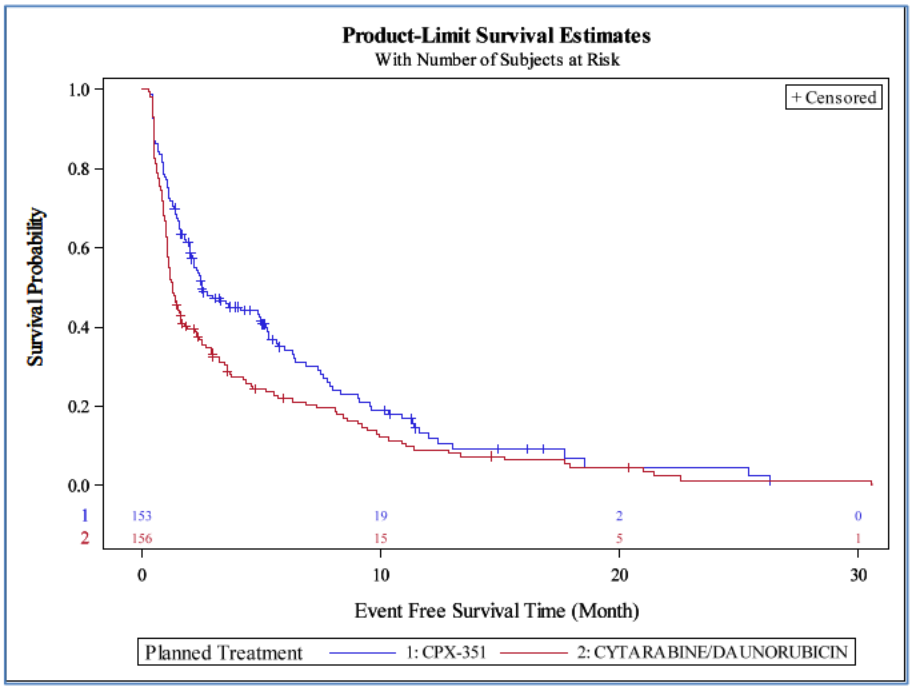
Table 21: Event Free Survival (Primary Analysis), ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)
Events, n (%)	32 (20.9)	13 (8.3)
Censored, n (%)	121 (79.1)	143 (91.7)
Median time, months (95% CI)	2.5 (2.1, 5.0)	1.3 (1.1, 1.6)
HR (95% CI) [a]	0.74 (0.58, 0.96)	
2-sided p-value [b]	0.02	

[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with

documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).
[b] The 2-sided p-value is based on a stratified log-rank test with the same stratification factors as the above Cox proportional hazards model.
Source: FDA reviewer analysis

Figure 17: Kaplan Meier Curve of Event Free Survival (Primary Analysis), ITT, Study 301



Source: FDA reviewer analysis

Event Free Survival – Sensitivity Analysis

Sensitivity Analysis 1: Define induction treatment failure as no CR or CRi in induction and use the date of death as the date of induction treatment failure, then defined the EFS as the time from study randomization to the date of induction treatment failure, relapse from CR or CRi, or death from any cause, whichever comes first.

Note this method uses the date of death as the event date for induction treatment failure. Earlier dates with marrow examinations showing no CR or CRi are not used to set the event date for ITF. Patients with induction treatment failure still alive at the time of analysis should be censored at the date of last assessment just as for patients who are surviving in CR or CRi.

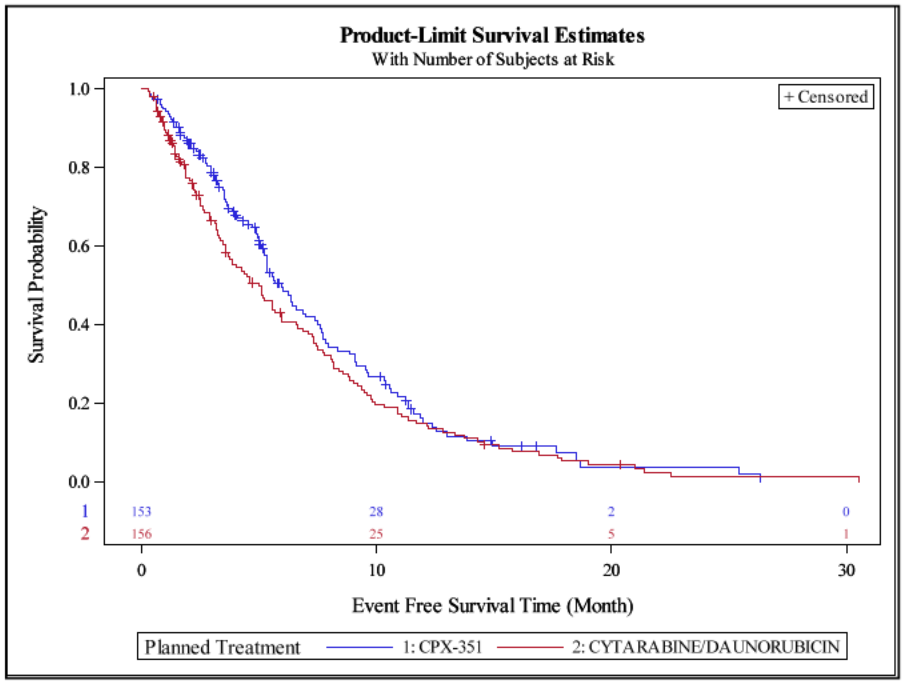
By this sensitivity analysis, the event free survival was not statistically significantly longer for patients in the CPX-351 arm than patients in the control arm (2-sided p value = 0.28). The median EFS was 6.0 months in the CPX arm vs 5.0 months in the control arm. The hazard ratio is 0.86 (95% CI = [0.33, 1.13])

Table 22: Event Free Survival (Sensitivity Analysis 1), ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)
Events, n (%)	111 (72.5)	133 (85.3)
Censored, n (%)	42 (27.5)	23 (14.7)
Median time, months (95% CI)	6.0 (5.2, 7.4)	5.0 (3.6, 5.9)
HR (95% CI) [a]	0.86 (0.66, 1.13)	
2-sided p-value [b]	0.28	

[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).
[b] The 2-sided p-value is based on a stratified log-rank test with the same stratification factors as the above Cox proportional hazards model.
Source: FDA reviewer analysis

Figure 18: Kaplan Meier Curve of Event Free Survival (Sensitivity Analysis 1), ITT, Study 301



Source: FDA reviewer analysis

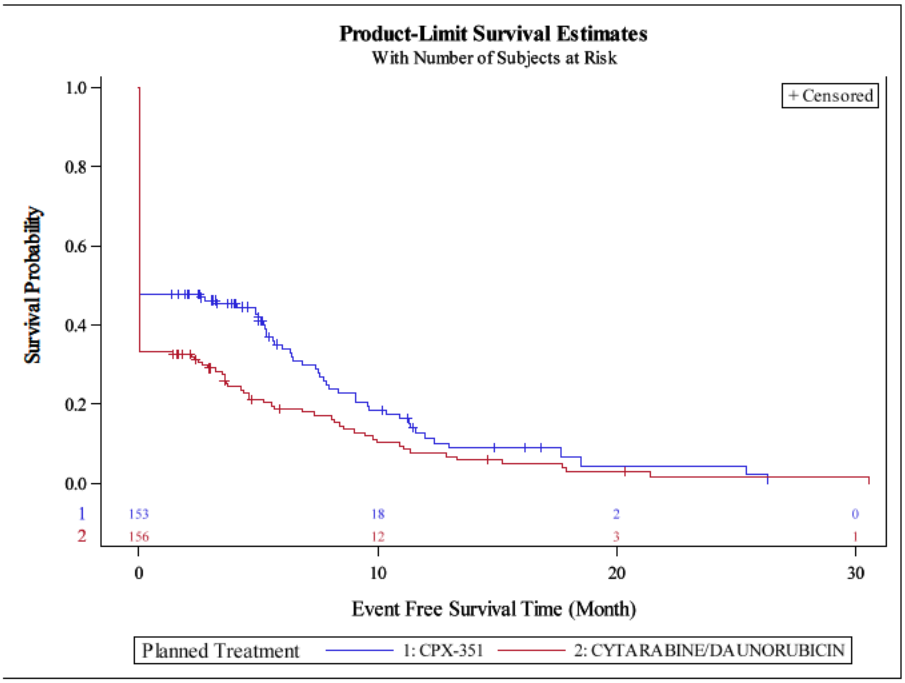
Sensitivity Analysis 2: Define induction treatment failure as no CR or CRi in induction and use study day 1 as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR or CRi, or death from any cause, whichever comes first.

Table 23: Event Free Survival (Sensitivity Analysis 2), ITT, Study 301

	CPX-351 (N = 153)	Control (N = 156)
Events, n (%)	122 (79.7)	143 (91.7)
Censored, n (%)	31 (20.3)	13 (8.3)
Median time, months (95% CI)	0.03 (0.03, 4.99)	0.03 (NE, NE)
HR (95% CI) [a]	0.78 (0.61, 1.00)	
2-sided p-value [b]	0.009	

[a] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by patients age (60-69 vs. 70-75) and AML type (treatment related AML vs. $_{MDS}$AML with documented history of MDS with prior treatment with hypomethylating agents vs. $_{MDS}$AML with documented history of MDS without prior treatment with hypomethylating agents vs. $_{denovo}$AML with karyotype characteristic of MDS vs. $_{CMMoL}$AML with documented history of CMMoL).
[b] The 2-sided p-value is based on a stratified log-rank test with the same stratification factors as the above Cox proportional hazards model.
Source: FDA reviewer analysis

Figure 19: Kaplan Meier Curve of Event Free Survival (Sensitivity Analysis 2), ITT, Study 301



Source: FDA reviewer analysis

Reviewer's Comments:

The definition of EFS has not been standardized , mainly due to the difficulty of assigning the

event dates for ITF. There are issues for both of the analyses of EFS presented here. The event dates for the primary EFS analysis was artificially defined at the end of induction treatment, therefore the KM estimates may have a sudden drop around 2 months for each treatment arm. Assigning the event date at death date for the ITF patients in the sensitivity analysis may appear less subjective, however, this analysis may artificially extend the timing of failure to respond to induction therapy. Various degrees of bias may be introduced based on numbers of patients who had the ITF in each treatment arm.

Additional Analyses Conducted on the Individual Trial

Subgroup Analysis of Overall Survival

Overall survival for subgroups of gender, race, age and geographic region was analyzed in the same manner as the overall ITT population. The event number, median of OS and hazard ratio were summarized in Table 24 below.

Table 24: Subgroup Analysis of Overall Survival by Demographic Characteristics, Study 301

	CPX-351		7+3		Hazard Ratio (95 % CI)
	Event n/N (%)	Median (95% CI)	Event n/N (%)	Median (95% CI)	
Age					
< 65	24/39 (61.5)	10.6 (5.0, NE)	30/41 (73.2)	9.2 (4.6, 17.9)	0.79 (0.46, 1.35)
≥ 65	80/114 (70.2)	9.1 (5.7, 12.0)	102/115 (88.7)	5.6 (4.0, 7.4)	0.59 (0.44, 0.79)
Gender					
Male	60/94 (63.8)	10.1 (6.4, 14.7)	86/96 (89.6)	5.6 (3.8, 7.8)	0.50 (0.36, 0.70)
Female	44/59 (74.6)	7.6 (5.4, 11.3)	46/60 (76.7)	7.2 (4.6, 10.9)	0.95 (0.63, 1.44)
Race					
White	88/128 (68.8)	9.6 (7.0, 12.0)	117/139 (84.2)	5.9 (4.9, 7.8)	0.63 (0.48, 0.84)
Black or African American	6/7 (85.7)	7.8 (1.6, 13.8)	4/6 (66.7)	9.0 (2.3, NE)	1.51 (0.42, 5.43)
Other	10/18 (55.6)	5.6 (3.6, NE)	11/11 (100)	5.9 (1.1, 12.8)	0.50 (0.21, 1.18)
Region					
US	96/144 (67.7)	9.6 (6.4, 12.0)	124/147 (84.4)	5.9 (5.1, 7.8)	0.65 (0.49, 0.84)
Canada	8/9 (88.9)	9.1 (2.6, 15.7)	8/9 (88.9)	3.8 (0.9, 8.8)	0.51 (0.19, 1.38)

Source: FDA reviewer analysis

The hazard ratios are all below 1, supporting the efficacy findings in the ITT population, except for the subgroup of black or African American, however, the number of patients and events are small, so the results are difficult to interpret.

Overall survival within subgroups of stratifications was analyzed in the same manner as the overall ITT population. The event number, median of OS and hazard ratio were summarized in Table 25 below. The hazard ratios are all below 1, supporting the efficacy findings in the ITT population.

Table 25: Subgroup Analysis of Overall Survival by Stratification Factor, Study 301

	CPX-351		**7+3**		**Hazard Ratio (95 % CI)**
	Event n/N (%)	Median (95% CI)	Event n/N (%)	Median (95% CI)	
Age					
60 – 69	62/96 (64.6)	9.6 (6.2, 12.6)	81/102 (79.4)	6.9 (4.6, 8.8)	0.68 (0.49, 0.95)
70 – 75	42/57 (73.7)	8.9 (4.7, 12.2)	51/54 (94.4)	5.6 (3.3, 7.5)	0.55 (0.36, 0.84)
AML Type					
CMMoL	8/11 (72.7)	9.3 (1.9, NA)	11/12 (91.7)	2.3 (0.7, 4.0)	0.37 (0.14, 0.95)
De novo AML with DMS karyotype	26/41 (63.4)	10.1 (5.7, 25.4)	29/37 (78.4)	7.4 (2.9, 13.8)	0.71 (0.42, 1.20)
MDS -> AML with prior HMA treatment	39/50 (78.0)	5.7 (3.5, 7.8)	47/55 (85.5)	7.4 (5.6, 9.4)	0.99 (0.64, 1.51)
MDS -> AML without prior HMA treatment	13/21 (61.9)	15.7 (5.6, NE)	16/19 (84.2)	5.1 (1.7, 11.1)	0.46 (0.22, 0.97)
Therapy-related AML	18/30 (60.0)	12.2 (7.4, NE)	29/33 (87.9)	5.9 (2.9, 8.5)	0.48 (0.26, 0.86)

Source: FDA analysis

Overall survival within subgroups of mutation type was analyzed in the same manner as the overall ITT population. The event number, median of OS and hazard ratio were summarized in Table 26 below. The hazard ratios are all below 1, supporting the efficacy findings in the ITT population.

Table 26: Subgroup Analysis of Overall Survival by Mutation Type, Study 301

	CPX-351		7+3		Hazard Ratio (95% CI)
	Event n/N (%)	Median (95% CI)	Event n/N (%)	Median (95% CI)	
NPM1					
Positive	6/13 (46.2)	19.2 (8.7, NE)	9/12 (75.0)	10.1 (2.5, NE)	0.45 (0.16, 1.28)
Negative	89/126 (70.6)	7.7 (5.6, 10.6)	115/132 (87.1)	5.5 (4.3, 7.4)	0.65 (0.50, 0.86)
FLT3					
Positive	17/22 (77.3)	10.3 (5.6, 14.9)	19/21 (90.5)	4.6 (1.6, 10.3)	0.54 (0.28, 1.05)
Negative	75/115 (65.2)	9.3 (5.7, 12.6)	101/118 (85.6)	5.8 (4.0, 7.8)	0.61 (0.45, 0.82)
CEBPA					
Positive	9/12 (75.0)	4.4 (1.5, NE)	5/5 (100.0)	2.9 (1.0, 3.7)	0.25 (0.07, 0.90)
Negative	82/123 (66.7)	9.6 (6.6, 12.2)	112/131 (85.5)	5.7 (4.6, 7.8)	0.61 (0.46, 0.81)

Source: FDA reviewer analysis

Finally, the HR was maintained between the arms regardless of the number of induction cycles, and whether or not patient received consolidation with the study drugs.

	CPX-351		7 + 3		Hazard Ratio (95% CI)
	n/N (%)	Median (95% CI)	n/N (%)	Median (95% CI)	
# of Induction Cycles					
0	0/0 (0.0%)	NA	5/5 (100%)	9.2 (1.9, 22.5)	NA
1	67/105 (63.8%)	11.3 (7.7, 14.7)	84/100 (84%)	5.5 (3.4, 7.8)	0.55 (0.40, 0.76)
2	37/48 (77.1%)	5.6 (3.6, 9.7)	43/51 (84.3%)	7.3 (5.1, 9.4)	0.96 (0.61, 1.49)
Whether Had Consolidation Phase					
Yes	25/49 (51.0%)	25.4 (12.4, NE)	25/32 (78.1%)	8.5 (5.7, 15.2)	0.44 (0.25, 0.77)
No	79/104 (76.0%)	5.4 (3.8, 7.8)	107/124 (86.3%)	5.1 (3.4, 7.3)	0.81 (0.61, 1.09)

Source: FDA reviewer analysis

Study 301 Efficacy Results Summary

Primary analysis showed that the overall survival was statistically longer in the CPX-351 arm compared with 7+3 arm. The median survival time was 9.6 months for the CPX-351 arm and 5.9 months for the control arm. The hazard ratio was 0.69 with 95% CI of [0.52, 0.90] with 2-sided p-value from the stratified log-rank test = 0.005.

Sensitivity analysis of overall survival on the impact of HSCT showed consistent results with the primary analysis results.

Subgroup analysis of overall survival by demographic characteristics and baseline disease characteristics also showed consistent results with the primary analysis in the ITT population.

Per the applicant's analysis, CR was achieved in 57 patients (37.3%) in the CPX-351 arm vs. 40 patients (25.6%) in the 7+3 arm. CMH test showed statistically significant difference (2-sided p-value = 0.04) between two treatment arm. By FDA's adjudication, CR was achieved in 59 patients (38.6%) in the CPX-351 arm vs. 43 (27.6%) in the 7+3 arm. CMH test result was not statistically significant (2-sided p-value = 0.053)

Analysis of other secondary endpoints showed supportive efficacy findings favoring the CPX-351 treatment arm.

In summary, the reviewer confirmed that CPX-351 therapy appeared to show favorable OS compared with 7+3 therapy in the Study CLTR0310-301.

Study 301 Statistical Issues

No major statistical issues were identified during the review. Minor issues include

- Discrepancy in the response assessment between the applicant and FDA. By the applicant, CR was achieved in 57 patients (37.3%) in the CPX-351 arm vs. 40 patients (25.6%) in the 7+3 arm. CMH test showed statistically significant difference (2-sided p-value = 0.04) between two treatment arm. By FDA after further adjudication, CR was achieved in 58 patients (37.9%) in the CPX-351 arm vs. 41 (26.3) in the 7+3 arm. CMH test result remains statistically significant (2-side p-value = 0.036).
- The definition of EFS has not been standardized which mainly due to the difficulty of assigning the event dates of induction treatment failure(ITF). There are issues for both of these analyses of EFS presented here. The event dates for the primary EFS analysis was artificially defined at the end of induction treatment, therefore the KM estimates may have a sudden drop around 2 months for each treatment arm. Assigning the event date at death date for the ITF patients in the sensitivity analysis may appear less subjective, however, this analysis may artificially extended the timing of failure to respond to induction therapy. Various degrees of bias may be introduced based on numbers of patients who had the ITF in each treatment arm.

Reviewer comment: It is noted that Study 301 used WHO 2008 criteria for eligibility, specifically for enrollment of AML with cytogenetic abnormalities characteristic of MDS. However, given the highly substantial rate of overlap between the two versions, the recommended indication for this approval is "t-AML or AML-MRC," as the latter categories encompasses the AML subcategories other than t-AML enrolled in Study 301.

7.2.3. CLTR0308-205

Trial Design and Endpoints

The pivotal trial CLTR0308-205 titled "a phase IIB, multicenter, randomized, open label trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus intensive salvage therapy in adult patients ≤ 60 years old with AML in first relapse following an initial CR > 1 month duration" is a randomized, open-label, parallel-arm trial.

Enrolled patients were 18-65 years of age with non-APL AML that had relapsed after a CR of at least 1 months duration. Patients had to have adequate renal and hepatic function and LVEF >50% at baseline. Patients were excluded if they had received >368 mg/m^2 prior cumulative anthracyline exposure, CNS disease, myocardial impairment, active infection, or Wilson's disease or other copper related disorder, or if they had experienced severe toxicity with conventional dose cytarabine during first line treatment.

Patients were randomized (2:1) to receive either CPX-351 or intensive salvage therapy. CPX-351 treatment was at a slightly higher dose and schedule than on Study 301, as the same dose was used for Induction and consolidation, namely:
Induction 1: 100 units/m^2 IV on days 1,3,5
Induction 2: 100 units/m^2 IV on days 1, 3
To be eligible for consolidation, patients had to have AE recover to grade ≤1 and a documented CR (including peripheral recovery of platelets and neutrophils) within 28-42 days of induction therapy. Patients achieving a CRi post induction were to consult with the sponsor regarding consolidation therapy.
Consolidation 1 and 2: 100 units/m^2 IV on days 1, 3.

On the control arm, investigators could choose any published regimen considered "standard" for salvage remission induction, including but not limited to:

Induction 1:

- High dose cytarabine (6-36 g/m^2 total dose) +/- an anthracycline
- 7+3 therapy, also slightly revised from that used in Study 205:
    - Cytarabine could be 100-200mg/m^2 continuous infusion x 7 days; daunorubicin 45-60 mg/m^2 IV on days 1-3, or equivalent anthracycline
- Mitoxantrone/etoposide based regimens (e.g.MEC: Mitoxantrone 8mg/m^2/day IV + Etoposide 100mg/m^2/day IV +Cytarabine 1000mg/m^2/day IV on days 1-5

Induction 2: any salvage therapy
Consolidation: investigator's choice (IC)

Randomization was stratified by the European Prognostic Index (favorable vs. intermediate vs. unfavorable).

The study was designed in two phases. In the treatment phase, patients received up to 2 induction courses and up to 2 consolidation courses and were intensively monitored for safety and secondary efficacy endpoints, including BM assessments on day 14 of the first induction, subsequently as required to confirm remission or persistent disease. The follow up phase begins after recovery from the last induction or consolidation course and continues for 1 year from randomization, and in the follow up phase, patients will be monitored for efficacy outcomes and survival.

The primary efficacy endpoint is the proportion of patients surviving at 1 year.

The secondary efficacy endpoints include complete remission (including CRi) rate and duration, event free survival, aplasia rate and rate of transfer for stem cell transplant.

EFS is defined as the time from study randomization to the date of relapse, initiation of non-protocol chemotherapy (e.g. salvage therapy) or death, whichever comes first. Patients transferred to transplant will be censored for EFS at the start of conditioning therapy.

Testing procedure was not specified in the protocol or SAP, therefore multiplicity was not controlled except for the primary endpoint. Note the study was designed with 2-sided alpha = 0.2. The SAP quote that "this study only seeks preliminary evidence of efficacy before proceeding to Phase III, where a much more stringent alpha would be used."

Statistical Analysis Plan

Analysis Population

Efficacy analysis set is defined as all patients who have received at least 1 dose of study drug. Sensitivity analyses for efficacy will also be performed for all patients randomized.

Reviewer comment:
Primary analysis population is not ITT population.

Sample Size and Power Considerations

The study were planned to enroll 120 patients with 2:1 randomization. This sample size has 83% power with 1-sided alpha = 0.1 to detect an absolute increase of 21% in survival rate at 1 year assuming the number of deaths at 1 year is binomially distributed and using a Chi-square test.

Analysis Method

The proportion of patients surviving at 1 year would be evaluated separately for each arm by the number of patients alive at 1 year divided by the total number of patients. A comparison between arms would be done using Fisher's Exact test.

Overall response (CR and CRi) will be summarized using frequency and percentages.

All time-to-event data would be analyzed separately for each treatment arm using the method of Kaplan Meier. Patients who achieve CR and are transferred for stem cell transplant as consolidation therapy would be censored for CR duration and EFS. The percentage of patients in CR transferred for stem cell transplant would be evaluated and reported separately for each arm.

Sensitivity Analysis

Efficacy analysis for the survival rate at 1 year would be performed for the randomized population.

Interim Analysis

No formal interim analysis was planned.

Protocol Amendments

Summary of Changes Related to Statistical Evaluation of Efficacy in Version 2.0

- Definition of Event free survival was changed from "time from randomization to treatment failure, disease relapse or death from any cause" to "time from study randomization to the date of relapse, initiation of non-protocol chemotherapy (e.g. salvage therapy) or death, whichever comes first. Patients transferred to transplant will be censored for EFS at the start of conditioning therapy".

- The statistical section clarified that although there is some risk in using a one-sided alpha of 0.1, it is important to note that this study only seeks preliminary evidence of efficacy before proceeding to Phase III, where a much more stringent alpha would be used.

- Clarified the hypothesis: Administration of liposome encapsulated cytarabine and daunorubicin at the synergistic 5:1 molar ratio in the form of CPX-351 will be superior to conventional intensive salvage therapy (high dose Ara-C +/- daunorubicin, "7+3", MEC, etc.) for the treatment of first relapse AML in patients age ≤ 60, and that the absolute difference in survival between the 2 study arms at 1 year willb e 21% or larger.

- Changed the order of secondary endpoint to CR (including CRi) rate and duration, EFS, rate of aplasia and rate of transfer for stem cell transplant

- Clarified that sensitivity analyses for efficacy will be performed for all patients randomized.

- Clarified that the primary endpoint the proportion of patients surviving at 1 year will be analyzed using Fisher's Exact test

Summary of Changes Related to Statistical Evaluation of Efficacy in Version 4.0

- Increase the patient's upper age limit to 65, and changed the title to "Phase IIB, multicenter, randomized, open label trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adult patients ≤ 65 years old with AML in first relapse following an initial CR> 1 month duration

- Added patients age 60-65 will be stratified separately, using the European Prognostic Index, which will ensure that patients over 60 will be balanced between the 2 arms.

7.2.4. Study Results

Compliance with Good Clinical Practices

The applicant stated in M2.5, section 1.7, that the CPX-351 development program has been carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki (2008), and standard operating procedures for clinical research and development at Celator Pharmaceuticals (a Jazz Pharmaceuticals company).

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in the appendix (0). The applicant submitted financial disclosure information from all of the investigators and subinvestigators from Studies 204, 205, 206 and 301; no financial interests or arrangements were reported for any of the investigators or subinvestigators .

Patient Disposition

A total of 126 patients were randomized in a 2:1 ratio to the CPX-351 arm (n = 81) and to the salvage therapy arm (n = 45). One patient in the salvage therapy arm withdrew consent prior to receiving study medication and was excluded from the efficacy evaluable analysis set and safety analysis set.

A summary of patient disposition on Study 205 was provided by the applicant and is depicted in Table 27. Overall, 57 (45.2%) patients completed the treatment phase (45.7% in the CPX-351 arm vs. 44.4% in the salvage therapy arm). For the patients who terminated study early, majority of them (35.7%) were due to persistent disease or lack of response (33.3% in the CPX-351 arm vs. 40.0% in the salvage therapy arm). The percentage of patients taken off treatment to receive stem cell transplant was 7.4% in the CPX-351 arm vs. 8.9% in the salvage therapy arm.

Table 27: Patient Disposition, Study 205

	CPX-351 N (%)	**Salvage** N (%)	**Total** N (%)
Patients randomized (ITT)	81 (100)	45 (100)	126 (100)
Patients who received study medication	81 (100)	44 (97.8)	125 (99.2)
Complete treatment	37 (45.7)	20 (44.4)	57 (45.2)
Terminate treatment early	44 (54.3)	24 (53.3)	68 (54.0)
Persistent disease/lack of response	27 (33.3)	18 (40.0)	45 (35.7)
Investigator discretion	6 (7.4)	2 (4.4)	8 (6.3)
Other – transplant	6 (7.4)	4 (8.9)	10 (7.9)
Other	3 (3.7)	0 (0)	3 (2.4)
Adverse event	2 (2.5)	0 (0)	2 (1.6)
Complete study	28 (34.6)	11 (24.4)	39 (31.0)
Terminate study early	53 (65.4)	34 (75.6)	87 (69.0)
Death	52 (64.2)	32 (71.1)	84 (66.7)
Lost to follow up	1 (1.2)	0	1 (0.8)
Consent withdrawn	0	2 (4.4)	2 (1.6)
Efficacy evaluable analysis set	81 (100)	44 (97.8)	125 (99.2)
Safety population	81 (100)	44 (97.8)	125 (99.2)

Source: Figure 1 and Table 11 in the Clinical Study Report for Study 205

Protocol Violations/Deviations

According to the applicant's analysis, there were 9 subjects on study who violated the inclusion criteria (3 in the CPX-351 arm vs. 6 in the salvage therapy arm). Of these, 3 subjects (1 in the CPX-351 arm and 2 in the salvage therapy arm) violated inclusion laboratory limits, 2 subjects (both in CPX-351 arm) were > 65 years of age, 3 subjects (all in the salvage therapy arm) had LVEF slightly below 50% at baseline, and 1 subject (salvage therapy arm) did not have pathological confirmation of relapsed AML after initial CR of > 1 month duration.

There were 12 subjects who violated the exclusion criteria (8 in the CPX-351 arm vs. 4 in the salvage therapy arm). Five subjects (3 in CPX-351 arm and 2 in salvage therapy arm) exceeded the maximum prior exposure to anthracycline therapy, 4 subjects (3 in CPX-351 arm and 1 in

salvage therapy arm) had received antineoplastic therapy within 4 weeks prior to study entry, 1 subject (CPX-351 arm) had an active second malignancy, and 2 subjects (1 CPX-351 arm and 1 in salvage therapy arm) had evidence of hypersensitivity to cytarabine, daunorubicin or liposomal products.

Demographic Characteristics

T

The median age of the patients was 52 years. Overall, there were slightly more female (56.8%) than male (53.1%) patients. The majority of patients were white (87.7% in the CPX-351 arm and 81.8% in the 7+3 arm).

Table 28: Demographic Characteristics, Efficacy Evaluable Analysis Set, Study 205

	CPX-351 (N = 81) n (%)	**Salvage** (N = 44) n (%)	**Total** (N = 125) n (%)
Sex			
Male	38 (46.9)	19 (43.2)	57 (45.6)
Female	43 (53.1)	25 (56.8)	68 (54.4)
Age			
Mean years (SD)	49.4 (11.6)	51.8 (11.5)	50.2 (11.6)
Median (years)	52.0	55.5	52.0
Min, max (years)	20, 66	20, 65	20, 66
Age Group			
< 60 years	68 (84.0)	34 (77.3)	102 (81.6)
≥ 60 years	12 (14.8)	10 (22.7)	22 (17.6)
Race			
White	71 (87.7)	36 (81.8)	107 (85.6)
Black or African American	8 (9.9)	6 (13.6)	14 (11.2)
Asian	1 (1.2)	2 (4.5)	3 (2.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.2)	0 (0.0)	1 (0.8)
Ethnicity			
Hispanic or Latino	7 (8.6)	4 (9.1)	11 (8.8)
Not Hispanic or Latino	74 (91.4)	40 (90.9)	114 (91.2)

Source: Table 12 in Clinical Study Report for Study 205

Table 29: Baseline Disease Characteristics, Efficacy Evaluable Analysis Set, Study 205

	CPX-351 (N = 81) n (%)	Salvage (N = 44) n (%)	Total (N = 125) n (%)
Time (month) since diagnosis			
Mean (SD)	15.1 (14.4)	13.4 (10.1)	14.5 (13.0)
Median	11.7	10.2	11.3
Min, Max	0.5, 109.4	2.9, 55.7	0.5, 109.4
Leukemia Type at Diagnosis			
De novo AML	71 (87.7)	41 (93.2)	112 (89.6)
Secondary AML	10 (12.3)	3 (6.8)	13 (10.4)
Cytogenetic Risk Category			
Favorable	8 (10.3)	4 (9.8)	12 (10.1)
Intermediate	47 (60.3)	25 (61.0)	72 (60.5)
Adverse	23 (29.5)	12 (29.3)	35 (29.4)
Chromosomal Abnormalities			
>= 3 abnormalities	15 (18.5)	8 (18.2)	23 (18.4)
< 3 abnormalities	48 (59.3)	23 (52.3)	71 (56.8)
Unknown	18 (22.2)	13 (29.5)	31 (24.8)
WBC (109/L) at baseline			
< 20	65 (80.2)	38 (86.4)	103 (82.4)
20 – 100	16 (19.8)	4 (9.1)	20 (16.0)
> 100	9 (0.0)	2 (4.5)	2 (1.6)

Source: Table 13 in Clinical Study Report for Study 205

Efficacy Results – Primary Endpoint

All primary efficacy analyses were based on all patients who have received at least 1 dose of study drug. The proportion of subjects surviving at 1 year was 35.8% in the CPX-351 arm vs. 27.3% in the salvage therapy arm. The difference was not statistically significant with p value = 0.43 from the Fisher's exact test using the efficacy analysis set.

Table 30: Survival at 1-year based on Efficacy Analysis Set (Primary Analysis), Efficacy Evaluable Analysis Set, Study 205

	CPX-351 N = 81	Salvage N = 44	2-sided p-value
Death, n (%)	52 (64.2)	32 (72.7)	0.43
Alive, n (%)	29 (35.8)	12 (27.3)	

Source: FDA reviewer analysis

The sensitivity analysis based on the ITT population showed consistent results with those in the primary analysis.

Table 31: Survival at 1 year based on ITT population (Sensitivity Analysis), Efficacy Evaluable Analysis Set, Study 205

	CPX-351 N = 81	Salvage N = 45	2-sided p-value
Death, n (%)	52 (64.2)	32 (71.1)	0.55
Alive, n (%)	29 (35.8)	13 (28.9)	

Source: FDA reviewer analysis

Time-to-event analysis of overall survival showed that the median of overall survival is 8.5 months in the CPX-351 arm and 6.3 months in the salvage therapy arm. The hazard ratio was 0.75 (95% CI [0.48, 1.16]).

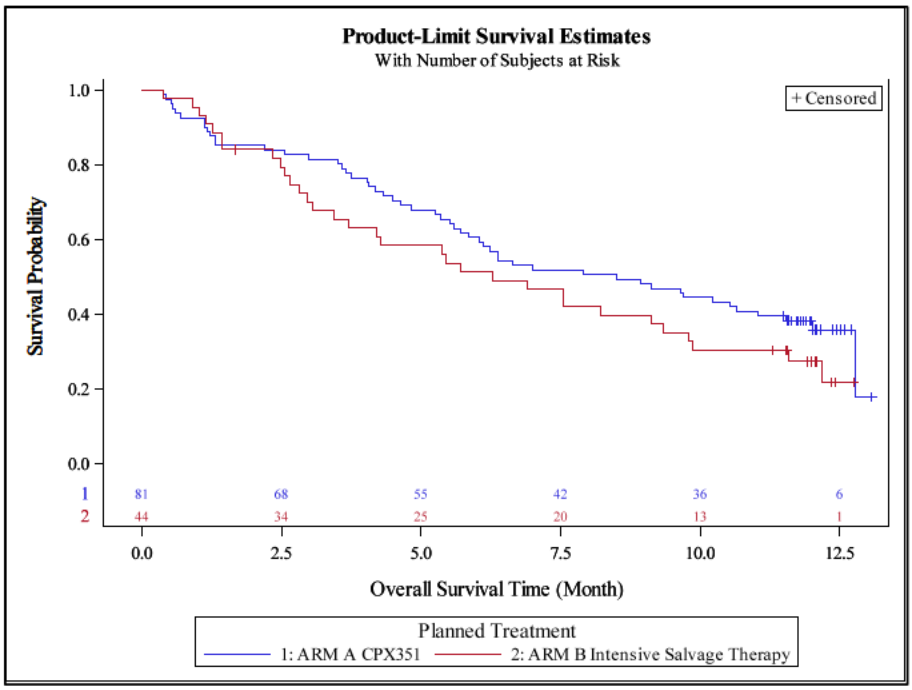
Table 32: Time-to-Event Analysis of Overall Survival, Efficacy Evaluable Analysis Set, Study 205

	CPX-351 (N = 81)	Control (N = 44)
Events, n (%)	52 (64.2)	32 (72.7)
Censored, n (%)	29 (35.8)	12 (27.3)
Median time, months (95% CI)	8.5 (5.8, 11.0)	6.3 (3.4, 9.3)
HR (95% CI) [a]	0.75 (0.48, 1.16)	

Source: FDA reviewer analysis

The Kaplan Meier curves of overall survival are plotted in the following figure.

Figure 20: Kaplan Meier Curves of Overall Survival, Efficacy Evaluable Analysis Set, Study 205



Source: FDA reviewer analysis

Reviewer Comments

The study 205 was designed with insufficient power, which made the analysis results difficult to interpret. There is insufficient data to assess whether there is insufficient power to detect the treatment effect or the study drug is ineffective in the study population

Reviewer Comment: Study 205 did not meet its primary endpoint, (b) (4) (b) (4) ***However, a limitation of use is not warranted, since as discussed above, the study was designed with insufficient power to detect a treatment effect, such that the failure to achieve the primary endpoint may be a matter of small numbers rather than actual lack of clinical benefit. Further, the OS trend is still favorable towards the CPX-351 arm. Finally, since there is no evidence from this study that patients treated with CPX-351 in this studied patient population do worse than with standard induction, this study need not be used to support a limitation of age in the indication statement. As long as the safety profile is acceptable in patients 18-60 years of age (7.4.4, 7.4.6), based heavily on this study, all adults may be included in the indication.***

Study 205 Efficacy Results Summary

The proportion of subjects surviving at 1 year was 35.8% in the CPX-351 arm vs. 27.3% in the salvage therapy arm. The difference was not statistically significant with p value = 0.43 from the Fisher's exact test using the efficacy analysis set.

Study 205 Statistical Issue

Study 205 was designed with insufficient power, which made the analysis results difficult to interpret. There is insufficient data to assess whether there is insufficient power to detect the treatment effect or the study drug is ineffective in the study population.

7.2.5. Study CLTR0308-204

Study 204: Study Design

Study 204 was a Phase 2 multicenter, randomized (2:1) , open-label, study of CPX-351 vs standard induction therapy with 7+3. Patients had to be between the ages of 60-75 years of age with newly diagnosed AML, including but not limited to t-AML or AML with an antecedent hematologic disorder. They had to have an ECOG PS of 0-2, and adequate organ function as defined in the pivotal study. Patients with APML, favorable cytogenetics, prior anthracycline exposure of >368 mg/m^2 daunorubicin equivalent, CNS involvement, myocardial impairment, uncontrolled infection, or Wilson's disease or other copper-related disorder were excluded. Randomization was stratified by categorization to standard and high risk based on AML type, age and cytogenetics , as follows:

Characteristic	Standard Risk	High Risk
AML type	de novo AML and	secondary AML or
Age	60 – < 70 years of age and	70 – < 76 years of age or
Cytogenetics	< 3 abnormalities	≥ 3 abnormalities

Source: Applicant's CSR for Study 204, section 9.4.3.2, page 28

Treatment on the CPX-351 arm was identical to that in Study 205 (7.2.3); 7+3 used cytarabine at 100 mg/m^2 and daunorubicin 45-60 mg/m2, at the same schedule described in 7.2.1. Patients in both arms could receive up to 2 cycles of induction and 2 cycles of consolidation.

The primary endpoint was CR rate as defined above during the induction period. Secondary endpoints included CRi, remission duration, EFS, OS at 1 year, aplasia rate, and rate of HSCT. The study had 85.5% power to detect an absolute difference of 23% in CR rates between the arms with a 1-sided alpha of 0.1. There was no adjustment for multiplicity for the secondary endpoints.

Study 204 allowed for crossover from the 7+3 arm to the CPX-351 arm for patients who had persistent AML after 2 inductions, or after one induction if they had "evidence of residual AML suggesting very low probability of response to second induction course of the "7 + 3" regimen." The latter category was not further defined in the protocol. Crossover was considered an event for EFS, and patients in the 7+3 arm had all response assessments with the exception of OS assessed before crossover.

Study 204: Results

Of the initial 127 randomized subjects, 126 were treated: 85 with CPX-351 and 41 with 7+3. Patients had a median age of 68, and two patients over the age of 75 were enrolled. Sixty five percent of patients had de novo AML and 35% had t-AML or AML with an antecedent hematologic disorder, 39% were standard risk based on the table above, 31% had adverse cytogenetics (NCCN guidelines), and the majority (57%) had an ECOG PS of 57%. These were relatively balanced between the arms.

In the CPX-351 arm, 36 patients (42%) completed treatment, a rate similar to that seen on the control arm with 18 patients (44%) completing treatment. Seventy –six patients (88%) on the CPX-351 arm and 33 patients (81%0 on the control arm enrolled in the 1 year follow-up phase. Ten patients (24%) from the 7+3 arm crossed over to receive CPX-351.

More patients on the control arm received 2 cycles of induction (29% vs 20%); more patients on the CPX-351 arm received at least one cycle of consolidation (27% vs 15%).

The primary endpoint, CR rate was the same for each arm (49%). There were also no significant differences in remission duration between the arms. EFS at 1 year was defined as the time from randomization to the date of persistent disease after baseline and before crossover, persistent disease or disease relapse (after CR), or death, and censored at HSCT. The median EFS for the CPX-351 arm was 161 days, compared to 55 days in the 7+3 arm, with a HR of 0.7 (95% CI: 0.5, 1.1). Median OS at 1 year could not be reliably estimated due to insufficient follow-up, and the observed HR was 0.89 (95% CI: 0.5, 1.6).

Reviewer comment: Study 204 was a negative study that did not meet its primary endpoint of at least a 23% difference in CR between the arms. There was no adjustment for multiplicity, such that the secondary endpoints cannot be interpreted to have statistical significance, even if they were positive. In any case, both EFS and OS had 95% confidence intervals for the hazard ratios that crossed 1. However, as with Study 205, there are no data from this study that would warrant a limitation of use. Given the mechanism of action of CPX-351, and its use of the same APIs as in the control arm, in liposomal form and at a fixed ratio, it is certainly plausible that it may confer a survival advantage in the subpopulation of patients with a dismal prognosis enrolled in Study 301, yet would not improve remission induction rates in a broader population of AML patients.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Methods

The applicant proposed the indication "For treatment of adults with (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)", (b) (4) The clinical development program for CPX-351 included three randomized trials for the treatment of patients with newly diagnosed (Study 301, Study 204) or relapsed/refractory AML (Study 205) , a phase 1 dose-ranging study (Study 101), and a PK Study (Study 206). The pivotal study (Protocol 301) was a randomized phase 3 study of CPX-351 versus 7+3 in patients 60-75 years of age with newly diagnosed t-AML or AML-MRC.

Since Study 301 was the only positive trial, the primary determination of efficacy is based on the results of Study 301, and Study 204 and Study 205 are considered supportive. Due to the differences in the patient populations, the studies were evaluated side-by-side and not pooled for any analysis in the integrated assessment.

Primary Endpoints

Table 33 shows an overall summary of the efficacy results for Studies 301, 204 and 205.

Table 33: Summary of Efficacy Outcomes

	Study 301 (Newly-Diagnosed)		Study 204 (Newly-Diagnosed)		Study 205 (First Relapse)	
	CPX-351 (n=153)	7+3 (n=156)	CPX-351 (n=85)	7+3 (n=41)	CPX-351 (n=81)	IC (n=44)
AML						
De novo	0	0	66%	63%	88%	93%
tAML/MRC	100%	100%	34%	37%	12%	7%
Median Age (yrs) (range)	68 (60-75)	68 (60-75)	68 (60-77)	68 (61-77)	52 (20-66)	56 (20-65)
Median OS	9.6 mos	5.9 mos	NE	NE	8.5 mos	6.3 mos
OS HR (95% CI)	0.69 (0.52, 0.90)		0.89 (0.5, 1.6)		0.75 (0.48, 1.16)	
Median EFS	2.5 mos	1.3 mos	5.2 mos	1.8 mos	2.5 mos	1.4 mos
EFS HR (95% CI)	0.74 (0.58, 0.96) [a]		0.7 (0.5, 1.1)		0.67 (0.4, 1.0)	
CR	38%	26%	49%	49%	38%	32%

Source: FDA analyses, Clinical Study Reports for CLTR0308-204 and CLTR0308-205
Abbreviations: IC, investigator's choice; NE, not estimable
[a] HR 0.78 (0.61, 1.00) when the induction failure event is assigned to the date of randomization.

OS was the primary endpoint for Study 301. Study 301 accrued 309 patients, and the median OS in the CPX-351 arm was 9.6 months (95% CI 6.6, 11.9) compared to 5.9 months (95% CI 5, 7.8) in the control arm, with a HR of 0.69 (95% CI 0.52, 0.9) and a 2-sided stratified long-rank p-value of 0.005, indicating a survival benefit with CPX-351 treatment in this population.

In Study 204, there were an insufficient number of patients with newly-diagnosed t-AML and AML-MRC to determine if the results in that subgroup was supportive of the OS finding in Study 301, but it was clear that Study 204 overall did not support the use of Vyxeos for treatment of all types of AML. Additionally, the results of Study 205 showed no survival benefit of Vyxeos over investigator's choice of salvage therapy for patients with AML in first relapse.

Secondary and Other Endpoints

Table 33 also shows the results for EFS and CR for Studies 301, 204 and 205. CR was the first secondary endpoint with alpha control in Study 301. The CR rate was significantly higher in the Vyxeos arm compared to the control arm in this study. There was no significant different between the CR rates on the arms on Studies 204 or 205. However, there was no trend suggesting worse CR in the Vyxeos arm on either of these 2 randomized trials.

EFS was an additional secondary endpoint in Study 301. Inference testing was not implemented, since alpha was already spent; however, once again the trend across protocols suggested that there was at least no adverse impact on EFS in the Vyxeos arms.

Subpopulations

Since Study 204 and Study 205 were negative trials, the assessment of efficacy within subpopulations was applicable only for Study 301. The direction of the treatment effect was consistent over the subgroups in Study 301 for the baseline factors of age, gender, race, ethnicity, stratification factors and mutation types.

Additional Efficacy Considerations

Study 101 was an open-label single-arm dose-escalation trial of Vyxeos for patients with relapsed or refractory acute leukemia or higher-risk MDS. Vyxeos was studied in 10 cohorts receiving 3 - 134 units/m^2 days 1, 3 and 5 in cycles of no less than 28 days. AML was the diagnosis for 90% of the study population. The median exposure was 1 cycle (range, 1-3 cycles) for the overall population and 2 cycles (range, 1-2 cycles) for those treated with 101 units/m^2. The CR rate reported by the applicant was 14% (3/21) for the cohorts with doses of 3 - 76 units/m^2, 26% (5/19) for the 101 units/m^2 cohort, and 33% for the 134 units/m^2 cohort, suggesting a potential dose-response relationship. However, there was no formal dose-ranging study that assessed efficacy in patients with newly diagnosed t-AML or AML-MRC.

7.3.2. Integrated Assessment of Effectiveness

The efficacy of CPX-351 in newly diagnosed t-AML and AML-MRC has been established, primarily based on the results of the randomized, phase 3 pivotal study, Study 301, in which patients 60-75 years of age with newly-diagnosed AML of these subtypes had longer OS compared with those treated with standard (7+3) induction therapy (HR 0.69, p=0.005). Since the biology of t-AML and AML-MRC are fairly consistent across the adult population, this efficacy outcome can be extrapolated to the full adult population.

(b) (4)

the limited interpretability of Study 205, namely its design with insufficient power to detect an OS treatment effect, makes a limitation of use unwarranted.

7.4. Review of Safety

Safety Review Approach

The review of safety for CPX-351 was primarily based on data from the pivotal Study 301, with support from the other trials listed in Table 9. Specifically, extension of the indication to include adults under the age of 60 relied upon results from Study 205, and to a lesser extent Studies 101 and 206. Pooled safety data from the all studies using CPX-351 or from patients treated with CPX-351 at the proposed dose and schedule are discussed where relevant in this section.

7.4.2. Review of the Safety Database

Overall Exposure

Across the development program for CPX-351, 403 patients received at least one dose of CPX-351 on studies 101, 204, 205, 206 or 301. Twenty eight of these patients received a dose lower than that proposed by the applicant for this indication, all on Study 101 (see Section 7.4.7 for details regarding study design and dose dependency for adverse events). Based on results of Study 101, a phase 1 dose escalation study, the original dose for CPX-351 during both induction and consolidation dose was determined to be 100 unit/m^2 (the MTD was 101 units/m^2 , which, per the applicant, was rounded to reduce the risk of prescribing and administration errors. The schedule in subsequent studies was Days 1, 3 and 5 during Induction 1, and Days 1 and 3 for Induction 2 and both Consolidation phases. The applicant states that further experience from phase 2 studies 204 and 205, specifically, severe thrombocytopenia and a case of fatal intracranial hemorrhage, led to a dose reduction for consolidation to 65 units/m^2 on the same schedule, based on the fact that the first CR in the phase 1 study was achieved at approximately half of this dose, and that this magnitude of decrease was expected to produce a measurable reduction in the duration of severe thrombocytopenia(M5.3.5.2; also 2.5, section 3.3).

A summary of patients exposed to CPX-351 at any dose across its clinical development program is depicted in Table 34. All studies were either single arm or against an active control; no placebo controlled studies were performed across the CPX-351 development program.

Table 34: Pooled Safety Database- Safety population, Size and Denominators

Clinical Trial Groups	CPX-351 (n=403)	Active Control (n=226)
Controlled trials conducted for this indication[1]	153	151
All other than controlled trials conducted for this indication[2]	84	n/a
Controlled trials conducted for other indications[3]	166	75

Source: FDA reviewer analysis
[1]Study 301; [2] Studies 101, 206; [3S]Studies 204, 205; Note: Other than 5 patients in Study 101, the other indications included in this table are all for AML, with variations that are relevant to efficacy (age, treatment naive vs relapsed/refractory, disease category (t-AML, AML-MRC etc.)) and safety, although to a lesser extent.

Of note, 10 patients randomized to the control arm on Study 204 crossed over to receive CPX-351 when they were assessed to have progressive disease, and are included in Table 34 above. The applicant performed an analysis for this study, as well as for the pooled safety population, that included these patients twice for the safety analysis: in the control arm for AEs that occurred before crossover and in the CPX-351 arm for AEs that occurred after crossover. These patients were omitted from the FDA safety analyses due to the confounding control treatment given within a relatively short window of time prior the CPX-351 therapy.

A summary of exposure to CPX-3251 in Study 301 and the pooled safety database is depicted in **Table 35**. Given the intermittent and limited administration of CPX-351, exposure is depicted as number of cycles of induction and consolidation; due to the variation in delivery of a 2nd induction cycle based on response, the total number of cycles does not necessarily represent the sum of the number of inductions and/or consolidations, and is provided for reference as well. Overall, the median number of induction cycles was 1, the median number of consolidation cycles for patients who received a consolidation cycle was 1 (for all patients, the median was 0, as only 70 patients in the pooled database received at least one consolidation cycle) , and the median number of total cycles was 1 (range 1-4). Patients in the pooled safety database received a median of 3 infusions of CPX-351 (range 1-9); Most patients received 3 (n=181) or 5 (118) infusions; 49 patients received 7 infusions, and 7 or fewer patients each received 1, 2, 6, 8 or 9 infusions. The median cumulative CPX-351 dose across the pooled safety population was 304 units/m^2 (range 100 – 881). In Study 301, the median number of induction cycles and consolidation cycles was 1 each, and the median number of total cycles was 2 (range 1-4), with a median cumulative CPX-351 dose of 430 units/**m^2** (range 100-767). Patients received a median of 5 doses of CPX-351 (range 1-9). Most patients received 3 (n=64) or 5 (58) doses, 26 patients received 7 doses, 4 patients received 9 doses and 1 patients received only 1 dose of CPX-351.

Table 35: CPX-351 Exposure, Safety Population

	Number of Induction Cycles		Number of Consolidation Cycles		Total number of cycles			
	1	2	1	2	1	2	3	4
Study 301 (n=153)	105 (69%)	48 (31%)	26 (17%)	23 (15%)	65 (42%)	59 (39%)	26 (17%)	3 (2%)
Pooled safety database (n=393) [a]	300 (76%)	91[c](23%)	73(19%)	42[c](11%)	201(51%)	134(34%)	52(13%)	6 (2%)

Source: FDA reviewer analysis
[a]Including patients receiving lower doses (101) and higher doses (101, 204, 205) than in study 301, and excluding the 10 patients from the control arm on Study 204 who crossed over to CPX-351
[c]2 patients on study 101 received a 3rd induction cycle; [c] 1 patient on study 206 received 3 consolidation cycles

In rare instances, patients who are noted as having received a particular cycle of therapy received fewer than the mandated number of doses of that therapy. On the CPX-351 arm, USUBJID (b) (6) received only the day 1 dose of induction cycle 1 and was removed from treatment due to an AE of grade 3 acute kidney injury. On the control arm, USUBJID (b) (6) in the control arm received only 2 of the 3 daunorubicin doses in first induction due to an AE of grade 3 pneumonia and grade 4 respiratory failure, USUBJID (b) (6) got 1 dose each of cytarabine and daunorubicin during induction 1 and then withdrew consent, and USUBJID (b) (6) did not receive the 3rd dose of daunorubicin in induction 1 due to an AE of grade 3 tumor lysis and DIC on study day 3. Also, 1 subject in each arm (USUBJIDs (b) (6) (CPX-351) and (b) (6) (control)) received cytarabine as consolidation instead of the protocol mandated CPX-351 or 5+2.

Only the 179 patients who received CPX-351 in studies 206 and 301 received the product at this proposed dose and schedule; an additional 196 patients (treated on studies 204 and 205) received it at the higher consolidation dose. Since the induction doses are the same, the safety data from these additional patients are pooled for some of the analyses below, to look for additional safety signals. The following populations are referred to in various sections of the safety review:

301-CPX- all patients who received at least one dose of CPX-351 (100 units/m^2) in study 301 (N=153); these patients are those proposed for inclusion in section 6 of the prescribing information.

301-controls- all patients who received at least one dose of 7+3 in study 301 (N=151); these patients are those proposed for inclusion in section 6 of the prescribing information, as the comparator group to 301-CPX.

CPX 100- all patients who received at least one dose of CPX-351 with a starting induction dose of 100 units, regardless of the consolidation dose (N=365)

CPX-ALL- all patients who received any dose of CPX-351, with the exception of the 10 patients who crossed over to CPX-351 treatment on Study (N=393)

Relevant characteristics of the safety population:

Table 36: Demographics of the Safety Population

	301-CPX N=153 n (%)	301-Control N=151 n(%)	301-Total (N=304) n(%)	CPX-100 N=365 n (%)	CPX-ALL N=393 n (%)
SEX					
Male	94 (61.4)	94 (62.3)	188 (61.8)	211(58)	230(58)
Female	59 (38.6)	57 (37.7)	116 (38.2)	154(42)	163(41)
AGE					
Median (years)	68	68	68	66	66
Min, Max (years)	60, 75	60, 75	60 ,75	20, 80	20, 81
AGE GROUP					
< 65	39 (25.5)	39 (25.8)	78 (25.7)	161 (44)	176(45)
≥ 65	114 (74.5)	112 (74.2)	226 (74.3)	204 (56)	217(555
RACE					
White	128 (83.7)	134 (88.7)	262 (86.2)	321 (88)	344(96)
Black	7 (4.6)	6 (4.0)	13 (4.3)	22 (6)	24(6)
Asian	6 (3.9)	2 (1.3)	8 (2.6)	9 (2)	12(3)
American Indian	1 (0.7)	0 (0.0)	1 (0.3)	1 (<1)	1(<1)
Other	11 (7.2)	9 (6.0)	20 (6.6)	12 (3)	12(3)
ETHNICITY					
Hispanic	7 (4.6)	7 (4.6)	14 (4.6)	24(7)	26(7)
Non-Hispanic	146 (95.4)	144 (95.4)	290 (95.4)	341(93)	367(9)
REGION					
United States	144 (94.1)	142 (94.0)	286 (94.1)	332 (91)	360(92)
Canada	9 (5.9)	9 (6.0)	18 (5.9)	19(5)	19(5)
Other	-	-	-	14(4)	14(4)
AML	(153100)	151 (100)	304 (100)	363 (99)	386 (98)
CPX- consolidation dose					
100 units/m2	-	-	-	61(17)	61 (15)
65 units/m2	49(32)	-	49 (16)	52(14)	52 (13)
n/a	104 (68)	151 (100)	255 (84)	252(69)	277 (70)

Source: FDA reviewer analysis

The demographics of the safety population on Study 301 as well as those of the various pooled safety populations are consistent with the demographics of t-AML and AML-MRC, with the exception of age, which was skewed towards the older population due restrictions of the eligibility criteria on the trials with the highest number of patients (204, 301). Although AML-MRC is more common in the older population such that these demographics generally represent those seen with this AML subtype, t-AML can occur in younger patients as well; a recent report from Spain reported a median age of 56 (range 17-78) in 231 patients with t-AML

(Santo et al, 2016). Similarly, the Danish registry study referred to above (Granfeldt Ostgard et al 2015) reported a median age of 58 for t-AML (range 22-76) and 62-64 for AML-MRC (18-87). Overall, these slight differences do not impact the applicability of the safety results in a significant way, as the safety of CPX-351 is for the most part improved in younger patients compared to older patients, as described in further detail in section 7.4.6 below.

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with CPX-351 therapy, and since it is a cytotoxic drug given over a specified interval, duration of therapy is not as relevant as it would be for chronically administered agents. The relatively high number of first induction cycles and patients who got only 1 cycle of therapy relative to those who completed therapy or got 2 or 3 cycles is high, such that the most informative data will be from the safety profile during induction. The randomization to active control which essentially consists of the APIs contained in CPX-351 allows for comparison to adverse reaction rates seen with 7+3 in non-liposomal form.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

On Study 301, all adverse events were collected as part of the protocol. However, prior to the version 2.3 amendment (finalized 11/04/2013, and implemented by the sponsor after IRB approval on 12/20/2013), certain AEs , specifically hospitalizations due to uncomplicated febrile neutropenia, grade 1-3 bleeding events in the presence or absence of platelet transfusion, and those due to disease progression, were exempted from SAE reporting. This exemption was removed based on Agency feedback. Studies 204 and 205 also included this exemption language.

As requested by FDA prior to NDA submission, the applicant attempted to ensure SAE capture in the application by:

- Reviewing all relevant AEs in the above categories from all studies and in the ISS and include in the datasets SAEs as reported as well as according to the regulatory definition (without the above exceptions)
- Performing an analysis of:
    - the number of patients treated prior to the protocol amendments removing the exemption language and after their implementation
    - The number of SAEs in patients treated before and after implementation of these amendments

Based on these analyses the number of patients treated on each protocol before and after amendment implementation is depicted in Table 37 below:

Table 37: Subject Incidence of SAEs Before and After Removal of Exception Language for SAE Reporting in Studies 204, 205 and 301

Study	Subjects completing treatment ***with*** exception language		Subjects completing treatment with ***no*** exception language		Subjects completing treatment with overlap (with and without) exception language	
	CPX-351	CONTROLa	CPX-351	CONTROLa	CPX-351	CONTROLa
301	70	66	70	72	13	13
SAE incidence	33 (47%)	21 (32%)	34 (49%)	28 (39%)	8 (62%)	7 (54%)
204[b]	5	2	57	27	33	12
SAE incidence	1 (20%)	-	26 (46%)	10 (37%)	20 (61%)	6 (50%)
205	47	28	16	11	18	5
SAE incidence	26 (55%)	11 (39%)	10 (63%)	6 (55%)	11 (61%)	2 (40%)

Source: Adapted from Applicant's SCS, M2.7.4 Table 21, page 70
[a]Control arm = 7+3 in studies 301, 204 and investigator's choice of salvage in Study 205
[b]In the applicant's analysis, the 10 patients randomized to the control arm who crossed over the CPX-351 arm were included in both treatment arms for the analysis.
Source: Adapted from Applicant's SCS, M2.7.4 Table 21, page 70

Overall, 83/153 patients in Study 301 and 186 patients across the 3 clinical studies were treated with CPX-351 with the exception language in place during the entire treatment period or part of it, and 79/151 patients in Study 301 and 126 patients across the 3 studies were treated with control with the language in place.

The analysis above revealed no major difference between SAE incidence before and after the exception language was removed; the discrepancies that are depicted are in categories with very small numbers of patients that are unlikely to change the overall characterization for each trial or for the pooled safety population.

Finally, FDA's Office of Computational Sciences (OCS) performed an analysis of Study 301 specifically looking at TEAEs comparing seriousness criteria and the SAE flag for each event. Of the 6656 TEAEs on Study 301, only 35 AEs (0.5%) were detected that had seriousness criteria (causing disability, hospitalization, life-threatening etc.) but were recorded as AESER=N (i.e., not flagged as SAEs). These AEs occurred in 24 patients (8%), 11 (7%) on the CPX-351 arm and 13 (9%) on the 7+3 arm.

Reviewer comment: Taken together, these analyses support the adequacy of SAE capture in the datasets provided.

The narratives submitted as part of the initial application were of poor quality with little if any data to supplement that already included as part of the ADSL, ADLB and ADAE datasets. They also contained some data that were inconsistent with these datasets (grades of AEs, numbers

of inductions received etc.). FDA reviewed all patient narratives from study 301, and adjudicated all cases of death within 100 days of the last IP dose, as well as all cases of IP discontinuation, against the ADAE , ADSL and ADAE datasets as well as the eCRFs to confirm the root COD (PD vs AE vs unknown vs other) and reason for treatment discontinuation. Additionally, applicant responses to Agency IRs were used for the FDA adjudication, when they provided relevant information. In some cases, blatant discrepancies between the narratives and the datasets were found. For example, USUBJID (b) (6) is described in the narrative as being alive as of day 586 (calculated to be (b) (6) by this FDA reviewer). However, in the ADSL dataset, the DTHFL is "yes," and the date of death is given as (b) (6). Upon review of the CRF, the date of death is confirmed, and the response to the Agency IR regarding this patient confirmed this. The Agency also reviewed all narratives for non-PD deaths from trials 101, 204, 205 and 206.

In general, in the ADAE dataset for Study 301, the variables "AEOUT" and "AEACN" were often unreliable. There were 60 patients for whom an AE whose toxicity was graded as a 5 (fatal), yet who had an AEOUT of "recovered/resolved," in 3 cases with the caveat "with sequelae." Further, even for non-fatal AEs, the AEACN was sometimes listed as "dose not changed" even in situations where it was clear that the treatment was stopped due to this AE. For example, patient (b) (6) achieved a CR on day 72 after 2 inductions on the CPX-351 arm. However, he was removed from the study on study day 75 ((b) (6) due to "further treatment rendered unacceptable by investigator," which was coded as "physician decision" by the applicant. He proceeded to treatment with cytarabine and decitabine according to the narrative on study day 78, 3 days after removal from study therapy. It is noted that he experienced multiple AEs and SAEs during treatment, including grade 3 febrile neutropenia on study day 50 and grade 4 myocardial infarction on study day 53, in addition to a grade 3 "skin lesion" on study day 9 and multiple other grade 1-2 AEs. All AEs are listed as AEACN "dose not changed," but it appears from the totality of the data that he was removed from study treatment due to AEs.

Reviewer comment: wherever possible, for study 301, FDA uses all available data and responses to IRs as detailed above to adjudicate relevant AE outcomes such as death and discontinuation of therapy. For the rest of the safety database, with the exceptions of deaths not in the setting of PD, FDA relied up on the applicant's assessment in the ADAE database for AE outcome.

Overall, since the information provided in the datasets, and used for the safety and efficacy analyses, appear to reflect the data in the CRFs, the limited interpretability of the narratives does not compromise the data integrity in a way that calls into question the reliability of the overall submission and analyses.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA. The version used across the development program differed, with version 8.0

used for Study 101, version 13.0 used for Studies 204 and 205, and version 16.0 for Studies 206 and 301. For the pooled safety population, the applicant recoded AEs for all studies using MedDRA version 16.1. Terms that referred directly to relapse, persistence or progression of the primary AML were excluded from the analyses. Where indicated in the tables or text, some adverse events are presented as grouped terms as defined in Appendix 9.2. Treatment-emergent adverse events (TEAE) excluded events that started and ended before start of study drug. For analyses other than deaths, TEAE were limited to those occurring only until 30 days after the last dose of study therapy.

Routine Clinical Tests

See7.2.1 for a description of the frequency of clinical assessments for the studies conducted in patients across the development program. The frequency of clinical assessments is adequate to assess the risks of serious safety signals.

7.4.4. Safety Results

Deaths

There were 234 patient deaths on trial 301, 106 (69%) on the CPX-351 ARM AND 128 (85%) on the control arm. FDA adjudicated causes of death by arm and time of death as related to treatment, as depicted in Table 38 below:

Table 38: Causes of Death, Study 301

	CPX-351 (N=153)	7+3 (N=151)
Overall	106 (69%)	128 (85%)
COD		
PD	83 (54%)	98 (64%)
AE	21[a] (14%)	23[b] (15%)
unknown	2 (1%)	7 (5%)
By day 30	9 (6%)	16 (11%)
By day 60	21 (14%)	32 (21%)
Within 30 days of last dose	15 (10%)	26 (17%)
COD		
PD	6 (4%)	16 (11%)
AE	9 (6%)	9 (6%)
unknown	-	1 (0.7%)
>30 days from last dose	91 (59%)	102 (67%)
PD	77 (50%)	82 (54%)
AE (excluding TRM)	6 (4%)	5 (3%)
AE (TRM)	6 (4%)	9 (6%)
unknown	2 (1%)	6 (4%)

Source: FDA analysis
COD: cause of death; PD: progressive disease; AE: adverse event; TRM: transplant related mortality; [a]include 6 cases of TRM;; [b]include 9 cases of TRM.

For study 301, there were 26 deaths regarding which FDA and the applicant agreed that the root COD was an AE (including TRM; 10 (7%) on the CPX-351 arm and 16 (10%) on the 7+3 arm) in the absence of PD. With the exception of 1 patient on the CPX-351 arm ((b) (6) for whom the applicant assessed that the root COD was unknown and in the absence of active leukemia, all patients that FDA assessed as having a root COD of PD, as depicted in Table 38 above, were assessed as such by the applicant as well. For 7 of the 9 patients for whom the FDA could not definitively assign a root COD ("unknown"), this was the case for the applicant as well; for both cases on the CPX-351 arm and 3 cases on the control arm, there was enough data from the datasets and eCRFs to ascertain that they were not in the presence of PD, and the applicant's assessment was the same. For 4 patients on the control arm, the FDA could not make an assessment as to whether they occurred in the presence or absence of active disease; the applicant root COD assessment for 3 of these patients was PD and for 1, not in the presence of active disease. For the remaining 18 deaths, the root COD as assessed by FDA and applicant are depicted in Table 39 below. The day of death in this table refers to the day relative to the last dose of study drug.

Table 39: FDA Adjudicated Root Cause of Death

Treatment arm	USUBJID	Day of death[a]	FDA root COD	Applicant root COD
CPX-351	(b) (6)	20	ICH	PD
		3	ICH	PD
		38	Infection (pneumonia)	PD
		93	TRM	PD
		51	Infection (sepsis)	PD
		7	Respiratory failure/TRALI	PD
		20	Infection (pseudomonal sepsis)	PD
		4	ICH	PD
		8	Infection (pneumonia, enterocolitis)	PD
		81	Infection (pneumonia)	PD
		20	Infection (sepsis)	PD
7+3		18	Infection (sepsis)	PD
		10	Respiratory failure	PD
		2	Infection (pneumonia)	PD
		64	TRM	PD
		13	Infection (septic shock)	PD
		2	Infection (fungal brain abcess)	PD
		1	Infection (sepsis) and cardiotoxicity	PD

Source: FDA analysis
COD: cause of death; TRALI: transfusion related acute lung injury; [a]day of death is relative to last dose of treatment.

Reviewer comment: It is recognized that some of the differences in root COD assessment are

due to the early date of death (for example days 3, 4 and 8 after the last dose of drug); for FDA, if there were no peripheral blasts on the day of death, and if there was a BM assessment done prior to the date of death, that assessment showed no blasts or blasts that were significantly decreasing, the possibility that the death could be related to the study drug could not be ruled out, and they were included in this assessment. For further details, see narratives below.

Details regarding the15 deaths on the CPX-351 arm where the FDA could not rule out the possibility that they were related to CPX-351 (including those from Table 40 above that were not due to TRM) are detailed here:

USUBJID (b) (6) was a 64 year old male with $_{MDS}$AML who had received prior HMA treatment for underlying CMMoL. He had poor risk cytogenetics and no baseline comorbidities. He had 22% BM blasts at screening, and 0.03 x 10^9/L peripheral blasts (an estimated 2% of his screening WBC count). He received his first dose of CPX-351 on (b) (6), and a BM on day 14 (b) (6)) showed less than 5% cellularity with no blasts reported. He remained severely neutropenia and thrombocytopenic (platelets 8 x 10^9/L on (b) (6) and 5 x 10^9/L on (b) (6), the day of the last CBC provided in the ADLB dataset) throughout. He developed multiple AEs including grade 3 sepsis and hypertension (the latter resolved 1 day prior to death), grade 4 hypotension and ultimately grade 5 cerebral hemorrhage on (b) (6).

Reviewer comment: the disappearance of BM blasts on day 14 in the absence of peripheral count recovery (which would not be expected that early in induction) does not allow for conclusive assessment of response; however, it does preclude the definitive assessment that the early death due to cerebral hemorrhage in the setting of thrombocytopenia was due to progressive disease and not toxicity of the study drug.

USUBJID (b) (6) was a 69 yo female with t-AML (breast and uterine CA, >12 years prior to AML diagnosis). She had poor risk cytogenetics but no notable co-morbidities at enrollment. She had 70% BM blasts at screening, and received her first dose of CPX-351 on (b) (6). She experienced grade 1 AEs including facial flushing and rash on D3, constipation, left arm pain, coarse breath sounds bilaterally, and dried blood on nose through study day 8, and died of an ICH on study day 9. The last platelet count on study day 8 was 5,000 /mcl.

USUBJID (b) (6) was a 74 yo male with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS (decitabine). He had poor risk cytogenetics but no notable co-morbidities at enrollment. He had 20% BM blasts at initial AML diagnosis, 28d prior to treatment initiation; a repeat BM 6 d prior to initiation of CPX had 10% BM blasts. He received his first dose of CPX-351 on (b) (6) and experienced grade 3 transaminase elevation on day 14 of the study. A BM on day 10 of induction showed 15% BM blasts, and Induction 2 was started 6 days later on (b) (6) (study day 16). During induction 2, the patient experienced multiple grade 3 AEs including altered mental status (disorientation, confusion, delirium), chest pain, febrile neutropenia, anorexia, hypoxia, Cryptococcus fungemia and euthyroid sick syndrome, and grade 4 AEs including Stenotrophomonas maltophilia bacteremia, respiratory

failure and ultimately grade 5 Stenotrophomonas pneumonia on day 61. The last BM assessment prior to death ([(b) (6)]), performed on study day 34 [(b) (6)]) showed <5% cellularity with 0% blasts, and there were no blasts detected in the peripheral blood at any point during the study.

USUBJID [(b) (6)] was a 72 year old female with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS (azacitidine and decitabine). She had intermediate risk cytogenetics and no notable co-morbidities at enrollment. She had 64% BM blasts at diagnosis and received her first CPX-351 dose on [(b) (6)]. Her day 14 BM showed 11% blasts, and she received a second course of induction starting on [(b) (6)] Subsequent BMAs on day 14 ([(b) (6)]), day 28 ([(b) (6)]) and 42 ([(b) (6)]) all had <10% cellularity and 0-1% blasts. During her treatment, she experienced multiple grade3 AEs including febrile neutropenia at multiple times throughout the treatment, last from [(b) (6)] to [(b) (6)] per the ADAE dataset. She experienced multiple other grade 1-2 AEs throughout her treatment course, including grade 2 fungal pneumonia (onset, [(b) (6)]) and sepsis that was graded "grade 2" in the ADAE dataset (***Reviewer comment: it is noted that per CTCAE v4.03, there is only grade 4 sepsis, as the diagnosis itself is considered life-threatening)*** that began on [(b) (6)] and was coded as having recovered/resolved with an AE end date of [(b) (6)]; the patient was taken off study treatment on [(b) (6)], and died at home on hospice on [(b) (6)]. Per the applicant, the root COD was PD; given the totality of the data, this death is at least possibly due to an AE of sepsis. The patient was in a state of aplasia with no signs of progressive disease at the time of death.

USUBJID [(b) (6)] was a 75 year old female with $_{de\ novo}$AML who had AML-MRC. She had poor risk cytogenetics and no baseline comorbidities. She had 61% BM blasts at screening and received her first dose of CPX-351 on [(b) (6)]. She developed grade 1 fever on that day, and grade 4 transfusion-related acute lung injury (TRALI) on [(b) (6)], the day of the 2nd dose of CPX-351. She subsequently developed grade 1 diarrhea 3 days later, followed the next day by grade 2 acute renal failure, and was diagnosed with a palatal disorder and zygomycosis (both grade 2) on [(b) (6)]. She died on [(b) (6)], with a diagnosis of grade 5 TRALI. It is noted that her peripheral blood blast count on the first day of therapy was 2.8 x 10^9/L, which peaked at 6.4 x 10^9/L 2 days later, and then decreased to 2 x 10^9/L on [(b) (6)], 0.3 x 10^9/L on [(b) (6)] and ultimately 0 on the date the last labs were taken (per the ADSL dataset; [(b) (6)]). Her WBC count decreased as well from 27.7 x 10^9/L on the first day of treatment to 0.7 x 10^9/L on [(b) (6)].

Reviewer comment: It is not clear from the submission what the transfusion that caused the TRALI was, and it is at least possible that this was an infusion reaction to the CPX-351 infusion, the second dose of which was given on that day (See reviewer comment below regarding vital sign monitoring and infusion reactions). It is also noted that the hemoglobin was 8.4 g/dL and platelets 38 x 10^9/L on the day of the reaction, not numbers that necessarily trigger a red blood cell or platelet transfusion. Given the decreasing WBC and peripheral blast counts, indicating disease response, CPX-351 cannot be excluded as a possible cause of death for this patient.

USUBJID [redacted] was a 66 year old female with AML-MRC; she had poor risk cytogenetics and no baseline comorbidities. She had 38% BM blasts at screening and commenced treatment with CPX-351 on [redacted] She received 2 inductions and achieved a CR on [redacted] She had multiple AEs including grade 4 bacteremia and sepsis and grade 3 febrile neutropenia and clostridium difficile infection, as well as grade 3 mouth hemorrhage during her first 2 induction cycles, which reportedly recovered. On [redacted] during her second induction, she experienced grade 3 dizziness and fall; the dizziness resolved on [redacted] and she commenced consolidation on [redacted] with no peripheral blasts. She developed sepsis on [redacted] which was ultimately fatal on [redacted].

USUBJID [redacted] was a 71 year old female with t-AML after treatment for breast cancer. She had favorable cytogenetic risk (NPM1 mutation) and no baseline comorbidities. She had 60% BM blasts at screening and commenced treatment with CPX-351 on [redacted] She received all 3 induction doses on schedule, and she developed multiple grade 3-4 AEs within 4 days of treatment initiation, including grade 3 febrile neutropenia, pneumonitis hypertension and pleural effusion, and grade 5 pseudomonal bacteremia that led to her death on [redacted].

USUBJID [redacted] was a 65 year old female with t-AML after treatment for squamous cell carcinoma of the head and neck (HNSCC) treated with chemotherapy and radiation. She had poor risk cytogenetics and no baseline comorbidities. She had 25% BM blasts and 6% blasts in her peripheral blood at screening, and started CPX-351 treatment on [redacted] Her peripheral blood blasts peaked at 9% on day 3 of treatment, and then went down to zero; her platelet count on treatment was always at 5 x 10^9/L. She experienced grade 2 palmar-plantar erythrodysesthesia syndrome on [redacted] and post-procedural hemorrhage (not otherwise specified) on [redacted] the latter reportedly resolved on the same day. She developed grade 5 CNS hemorrhage on [redacted], the day of her death.

USUBJID [redacted] was a 61 year old male with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS (azacitidine and decitabine). He had intermediate risk cytogenetics and no baseline comorbidities. He had 67% BM blasts and 11% blasts in the peripheral blood at screening, and received his first dose of CPX-351 on [redacted] He did not have any further bone marrows, but there were no further peripheral blood blasts from the first day of treatment through his death on [redacted]. On [redacted] the patient developed grade 3 febrile neutropenia and pneumonia, grade 2 confusion and grade 3 hemorrhagic enterocolitis on [redacted] and ultimately grade 5 multi-organ failure on [redacted]

Reviewer comment: As was the case in for subject [redacted], there were no follow-up BM assessments for [redacted], such that whether there was the beginning of disease control is unknown; in the case of [redacted] the disappearance of peripheral blasts supports the notion that this was the case. As such, the role CPX-351 in these patients' deaths' cannot be ruled out.

USUBJID [redacted] was a 72 year old male with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS. He had intermediate risk cytogenetics and no baseline

comorbidities. He had 31% BM blasts at screening, and received his first dose of CPX-351 on (b) (6) He received 2 courses of induction, and multiple BM assessments, the last performed on (b) (6) showed <5% cellularity with no evidence of blasts. No evidence of peripheral blasts were included on labs through (b) (6) He experienced multiple AEs throughout the treatment course, and many were ongoing on the date of removal from study treatment ((b) (6) including multiple grade 1-2 AEs (grade 2 diastolic dysfunction and others) as well as grade 3 fall and angina pectoris and grade 4 respiratory failure. He ultimately died of grade 5 pneumonia diagnosed on his date of death (b) (6)).

USUBJID (b) (6) was a 63 year old with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS. He had intermediate risk cytogenetics and no baseline comorbidities. He had21% BM blasts at screening, and received his first dose of CPX-351 on (b) (6) His initial BM assessment on day 14 of induction showed 10% cellularity and 2% blasts, and he remained pancytopenic with an ANC of 280 x 10^6/L and platelet count of 18 x 10^9/L on his day of death ((b) (6)). During induction he experienced multiple AEs, including grade 3 febrile neutropenia that ultimately progressed to grade 5 sepsis, as well as grade 3 pneumonia and other grade 1-2 AEs, that were ongoing at the time of death.

The following 3 deaths on the CPX-351 arm were not assessed by FDA as likely related to CPX-351, but its contribution could not be ruled out entirely:

USUBJID (b) (6) was a 72 year old female with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS. She had intermediate risk cytogenetics and no baseline comorbidities. She had 90% BM blasts at screening, and received her first dose of CPX-351 on (b) (6) A BM on day 14 of induction 1 showed 36% blasts. She had no further BM examinations, and there were no blasts in the peripheral blood at any point from the day 14 BM and through the last reported CBC on (b) (6) She experienced grade 3 febrile neutropenia from (b) (6) and multiple grade 1-2 AEs including vomiting, headache and mental status changes from (b) (6) She was removed from the study, per the ADSL dataset and narrative for lack of efficacy, on (b) (6) she died on (b) (6) of disease progression grade 5 per the ADAE dataset as well as the narrative.

Reviewer comment: Given the patient's response (>50% reduction in blast percentage) on the day 14 marrow, she did not necessarily meet criteria for study removal for PD; further, if this was the reason for treatment discontinuation, it is unclear why there was a 20 day lag between the day 14 marrow and study removal. In the context of the AEs, which although low grade, included mental status changes which may be clinically significant, and the date of death relative to CPX-351 treatment, it is not possible to rule out the contribution of CPX-351 to the patient's death.

USUBJID (b) (6) was a 68 year old female with $_{MDS}$AML who had received prior HMA treatment for the underlying MDS (azacitidine). She had intermediate risk cytogenetics and an abnormal echocardiogram at baseline with a LVEF range of 50-55%. She had 93% BM blasts at screening, and received her first dose of CPX-351 on (b) (6) A BM on day 14 of induction 1

showed 76% blasts; she also experienced multiple grade 3 AEs including colitis, febrile neutropenia and neutropenic colitis starting (b) (6) and after, and the latter was ongoing when she died on (b) (6) (in the ADAE dataset, stated as "AE end date of (b) (6) Although she received salvage therapy with cladribine and cytarabine starting 20 days after CPX-351 was discontinued, and her death was in the setting of ongoing PD after this salvage therapy, it is noted that she was taken off the study on day 16, 2 days after the day 14 BM showed a slight reduction in blasts, with a verbatim term for "TRTEREAS" of "unacceptable toxicity."

Reviewer comment: This reviewer's assessment is that disposition from treatment was AE, and root COD was PD, but there is not enough information to rule out the contribution of the AE from the CPX-351 to the patient's death

USUBJID (b) (6) was a 68 year old male with AML-MRC; he had poor risk cytogenetics and no baseline comorbidities. Screening BM showed 40% blasts, and he started treatment with CPX-351 on (b) (6) He had a 50% reduction in BM blasts on day 14 of induction 1, and proceeded to induction 2 five days later; BM assessment on day 14 of induction 2 on (b) (6) revealed 10% cellularity with 5% blasts, and no peripheral blasts. During both inductions he experienced multiple AEs including, beginngon on (b) (6) grade 3 fungal sinusitis, grade 4 hypoxia, and subsequently grade 4 pulmonary edema, sepsis and pulmonary alveolar hemorrhage that continued through her death on (b) (6), attributed to grade 5 sepsis.

Reviewer comment: Although the patient did not achieve a response, the borderline blast count on (b) (6) did not prompt removal from study therapy, it represented a decrease relative to the prior assessments and per the protocol, it could have been repeated 5-7 days later for confirmation of response or lack thereof. The multiple AEs that ultimately led to the patient's death must be seen as possibly in the context of progressive disease but not necessarily so, such that the contribution of CPX-351, the last dose of which was given 33 days prior to development of these AEs, cannot be ruled out.

The 15 deaths due to AEs on Study 301 that were not considered by FDA to be TRM nor in the setting of PD are summarized in Table 40 below:

Table 40: Non-TRM, Non-PD Causes of Death, by Arm, Study 301

	CPX-351 (N=153)	7+3 (N=151)
Within 30 days of last dose		
CNS hemorrhage	3 (2%)	1 (0.7%)
Infection	5 (3%)	7 (5%)
Respiratory failure	1 (0.7%)	1 (0.7%)
> 30 days from the last dose		
Infection	5 (3%)	3 (2%)
CNS hemorrhage	1 (0.7%)	-
Cerebellar herniation	-	1 (0.7%)
Cardiopulmonary arrest	-	1 (0.7%)

Source: FDA reviewer analysis

While the detailed descriptions above pertain to only patients treated with CPX-351, as part of the safety review, an analysis of reasons for discontinuations and death, including comparisons between the ADSL and ADAE datasets and the patient narratives was performed by FDA for the control group as well, to allow for a balanced comparison between the arms (see Table 38 and Table 39 above as well as Table 11, disposition). It is noted that there were discrepancies between the various data sources for these patients as well. For example, USUBJID (b) (6) a 67 year old female who was treated on study for CMMoL that had previously been treated with azacitidine and had no baseline comorbidities, was reported in the narrative to have received 1 induction course of 7+3 "and did not respond. The subject was taken off the study on Day 21." In the ADLB dataset, her day 14 BM had 20% cellularity and <5% blasts, a reduction of >50% as compared to her baseline BM (83% blasts), and no peripheral blasts from this date forward. She had multiple grade 3-4 AEs between days 9 and 21, her date of death, including ultimately grade 5 respiratory failure in the setting of fungal pneumonia and small intestinal obstruction, and none of these AEs had resolved at the time of death. Per FDA, root COD is assessed as possibly related to the control treatment.

Reviewer comment: While it is clear that CPX-351 treatment can lead to fatal ARs, the nature and timing of these toxicities are not particularly dissimilar from those seen with 7+3 induction therapy, and the rates of early (day 30 and day 60) mortality are lower in the CPX-351 arm. A warning and precaution regarding hemorrhagic events is warranted, given the proportion of fatal non-PD on treatment AEs that were due to hemorrhage, specifically CNS hemorrhage, the overall risk: benefit ratio of CPX-351 appears favorable .

Among the remaining 250 patients treated with CPX-351 across the clinical development plan, there were 137 deaths. These included 15 deaths within 30 days and 31 deaths within 60 days of initiation of treatment, respectively. Twenty nine deaths occurred within 30 days of the last dose of CPX-351 (range 6-30), and the remainder occurred more than 30 days from the last dose (range 31-644). The sponsor attributed 98 of these deaths to be in the presence of active leukemia, and the remaining 39 to be not in the presence of active disease. An additional 5 of these deaths were in the post-allogeneic HSCT setting, and thus considered TRM. Of the remaining 34 non-PD, non-TRM deaths, 8 occurred within 30 days of the last dose of CPX-351, 5 occurred between days 30 and 100 after the last dose, and 21 occurred between 102 and 323 days after the last dose of CPX-351. FDA reviewed the available narratives, CRFs and datasets for the 13 non-PD, non-TRM deaths as assessed by the applicant that occurred within 100 days of the last dose of CPX-351. The FDA adjudication for COD for these patients is outlined in Table 41 below. In 2 of the 13 cases, FDA assessed the deaths to be in the setting of active disease, and not fatal adverse events. In most of the other cases, FDA agreed with the applicant's assessment. In situations where there were not enough data to delineate the root COD with certainty, but certain parameters (i.e. presence of absence of disease) are supported by the documentation, FDA root COD contains this level of evidence; these are marked with an "*" in the table. Since the applicant only presented root COD as in the presence or absence of active leukemia, presented in the table is the primary COD as assessed by the applicant, unless

specified otherwise.

Table 41: Root COD Analysis, Deaths in the Absence of PD and Within 100 Days of CPX-351 Treatment, Pooled Safety Population

Trial	USUBJID	CPX-351 dose	Day of death[a]	FDA Root COD	Applicant COD
101	(b) (6)	24 units/m2	28	Infection (RSV)	RSV
101		134 units/m2	34	Infection (septic shock)	Septic shock
101		76 units/m2	45	Hypoxia, non-PD, post another therapy*	Hypoxia
101		101 units/m2	27	PD	Death not in the presence of active leukemia[b]
204		100 units/m2	16	Infection (sepsis)	Sepsis neutropenia
204		100 units/m2	21	ICH	Intracranial herniation due to bleeding
204		100 units/m2	57	Infection (pneumonia)	pneumonia
204		100 units/m2	69	Infection (CMV pneumonitis)	Respiratory failure
205		100 units/m2	92	TRM	"non PD, cancer-related organ failure"
205		100 units/m2	22	Infection (bacteremia)	bacteremia
205		100 units/m2	22	Infection (Febrile neutropenia)	Neutropenic fever, respiratory failure
205		100 units/m2	6	PD	"non PD, cancer-related organ failure"
205		100 units/m2	11	Sudden cardiac death	Sudden cardiac death

Source: FDA reviewer analysis
[a]Relative to last dose; [b]Although the applicant's root COD was presented as such, under primary COD, the applicant listed "progressive cancer."

Reviewer comment: the deaths in the ISS were consistent with those seen in Study 301, with infection as the most common cause of on-treatment death not in the setting of PD.

Serious Adverse Events

The limitations of analysis of SAEs in the application were described above in detail (Section 7.4.3). Since overall the reliability for detecting SAEs appears to be adequate despite these limitations, FDA performed an analysis of SAEs in Study 301, and in the pooled safety population.

In Study 301, 149 patients had at least one SAE, including 81 (53%) on the CPX-351 arm and 61 (40%) on the control arm. SAEs that occurred in ≥ 5% of patients on the CPX-351 arm are depicted in Table 42 below.

Table 42: SAEs by Preferred Tern on Study 301

	All grades				Grades 3-5			
	CPX-351		7+3		CPX-351		7+3	
PT[a]	N=153		N=151		N=153		N=151	
Dyspnea	18	12%	12	8%	18	12%	12	8%
Non-conduction cardiotoxicity	16	10%	19	13%	13	8%	17	11%
Sepsis (except fungal)	15	10%	9	6%	15	10%	9	6%
Pneumonia (except fungal)	12	8%	9	6%	12	8%	8	5%
Febrile neutropenia	12	8%	8	5%	12	8%	8	5%
Bacteraemia (except sepsis)	11	7%	6	4%	11	7%	6	4%
Haemorrhage	9	6%	9	6%	8	5%	6	4%

Source: FDA reviewer analysis
[a] Includes grouped terms (see Appendix 13.5)

The only SAE with a risk difference of ≥3% in the CPX-351 arm that is not represented on the table above is syncope, which occurred at a rate of 3% in the CPX-351 arm and not at all in the control arm.

Across the development program, 209 (57%) of the 365 patients who received CPX-351 at the proposed dose and schedule had at least one SAE. SAEs that occurred >1% of the pooled safety population included sepsis (excluding fungal; 13%), febrile neutropenia (11%), dyspnea (9%), non-fungal pneumonia (8%), non-conduction disorder cardiotoxicity (7%), hemorrhage (6%), bacteremia (excluding sepsis; 5%), pyrexia (3%), and fungal infection, renal insufficiency and cellulitis, each of which occurred in 2% of the pooled safety population. The preceding terms, with the exception of pyrexia, cellulitis, are the same SAEs that occurred at a grade of ≥3 in >1% of the pooled safety population.

Reviewer comment: The percentages described are smaller than what would be expected from intensive chemotherapy for AML, such that the limitation of SAE reporting as described in Section 7.4.3*Error! Reference source not found.* ***above needs to be kept in mind while interpreting these data. Nonetheless, the SAEs that occurred in Study 301 are consistent with the safety profile of CPX-351 as described elsewhere in the safety review. Also, there are data***

to support the fact that data from analysis of AEs by severity is more informative than the analyses by SAEs (Smit et al JCO 2017), such that less rigorous analysis of SAEs is not expected to cause a safety signal to go undetected.

Dropouts and/or Discontinuations Due to Adverse Effects

In study 301, the applicant reported that 13 AEs that led to treatment interruption or discontinuation; this included 7 AEs in 6 (4%) patients on the CPX-351 arm and 6 AEs in 4 patients (3%) on the control arm. AEs leading to discontinuation in CPX-351 as assessed by the applicant included cardiotoxicity (cardiac failure and cardiomyopathy in 2 patients each) and renal failure, and those leading to interruption included pericarditis and atrial fibrillation in 1 patient, and bacteremia and hypersensitivity in 1 patient each. On the control arm, 2 patients had treatment discontinued due to cardiotoxicity (LVEF decrease), and 2 patients had an interruption due to an AE: 1 due to localized edema, and another due to pulmonary hemorrhage in the setting of TLS.

FDAs review of the narratives, CRFs and datasets described above (7.4.3) yielded different outcomes for some of the adverse events as well. According to FDA analysis, 48 patients, 28 (18%) on the CPX-351 arm and 20 (13%) on the control arm had treatment discontinued due to an AE. A summary of discontinuations due to AEs based on this adjudication is summarized in Table 43 below together with a summary of AEs leading to interruptions/discontinuations in the pooled safety population, at any CPX-351 dose, excluding the 10 patients who crossed over to CPX-351 treatment on Study 204. The analysis for the remainder of the pooled safety population were done using the applicant's assessment in the ADAE dataset; only 6 patients had AEs for which the variable "AACN" was "drug withdrawn."

Table 43: TEAEs Leading to Treatment Discontinuation, Study 301 and the Pooled Safety Database

	Study 301		Pooled Safety
AE leading to treatment discontinuation	**CPX-351 N=153**	**7+3 N=151**	**Population N=393**
Total	28 (18%)	20 (13%)	34 (9%)
AEs, specified			
Cytopenias	9 (6%)	3 (2%)	9 (2%)
Thrombocytopenia	4 (3%)	2 (1%)	4 (1%)
Neutropenia	-	1 (0.7%)	-
Both	5 (3%)	-	5 (1%)
Infection	8 (5%)	8 (5%)	8 (2%)
Cardiotoxicity	1 (0.7%)	3 (2%)	1 (<1%)
Hemorrhage	1 (0.7%)	1 (0.7%)	2[a] (<1%)
Respiratory failure	3 (2%)	-	4 (1%)
Overall decline in performance/health	1 (0.7%)	2 (1%)	1 (<1%)

AE leading to treatment discontinuation	Study 301 CPX-351 N=153	Study 301 7+3 N=151	Pooled Safety Population N=393
Infection + cardiotoxicity	2 (1%)	2 (1%)	3[b] (<1%)
Infection + thrombocytopenia	-	1 (0.7%)	1 (<1%)
Colitis	1 (0.7%)	-	1 (<1%)
Temporal arteritis/visual impairment	1 (0.7%)	-	1 (<1%)
Renal insufficiency	1 (0.7%)	-	2 ((<1%)
Intermittent hypomagnesemia	-	-	1 (<1%)

Source: FDA reviewer analysis;
Discontinuations from the pooled safety population were not adjudicated by FDA, but are presented as described in the ADAE dataset of the ISS.
[a]Both of these were CNS hemorrhages
[b]This patient (USUBJID (b) (6)) also had concurrent grade 3 hypertransaminasemia, but given the pneumonia and pericardial effusion that were ultimately fatal, these cannot be assessed as related to the study drug.

Of note, FDA reviewed the CRF for the patient ((b) (6)) for whom the outcome withdrawn was given for grade 1 hypomagnesaemia; according to the investigator, the drug was withdrawn prematurely as the patient was in CRi and had intermittent hypomagnesaemia that was considered possibly related to CPX-351 treatment.

An additional 6 patients in the pooled safety population had their CPX-351 interrupted for TEAE. These included infusion related reaction, hyperbilirubinemia, nausea, pyrexia, infusion site extravasation and palpitations (1 patient each). The Hyperbilirubinemia and pyrexia were grade 3, and others were grade 1-2. All but the extravasation resolved.

Reviewer comment: While no new safety signal was detected in the analysis of discontinuations in the safety population, this needs to be taken with the limitations of the AACN variable across the application (Section 7.4.3 above).

Significant Adverse Events

For a detailed analysis of cardiotoxicity and other adverse reactions associated with the APIs contained in CPX-351, see section 7.4.5.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs on study treatment or within 30 days after its discontinuation occurred in all patients on Study 301. TEAEs summarized by System Organ Class that occurred at any point during treatment in more than 2 patients on the CPX-351 arm on Study 301 are summarized in Table 44 below.

Table 44: TEAE by SOC in >1% of CPX-351 Treated Patients, Study 301

	All grades				Grades 3-5			
	CPX-351		7+3		CPX-351		7+3	
System Organ Class	N=153		N=151		N=153		N=151	
Gastrointestinal disorders	139	91%	144	95%	23	15%	24	16%
General disorders and administration site conditions	132	87%	134	89%	24	16%	30	20%
Respiratory, thoracic and mediastinal disorders	126	82%	113	75%	38	25%	41	27%
Skin and subcutaneous tissue disorders	123	80%	96	64%	14	9%	7	5%
Infections and infestations	112	73%	103	68%	84	55%	77	51%
Blood and lymphatic system disorders	111	73%	108	72%	105	67%	108	72%
Nervous system disorders	101	66%	83	55%	18	12%	13	9%
Psychiatric disorders	79	52%	79	52%	7	5%	12	8%
Vascular disorders	78	51%	69	46%	28	18%	15	10%
Metabolism and nutrition disorders	72	47%	75	50%	7	5%	8	5%
Musculoskeletal and connective tissue disorders	70	46%	66	44%	7	5%	7	5%
Injury, poisoning and procedural complications	63	41%	49	32	7	5%	4	3%
Cardiac disorders	63	41%	61	40%	17	11%	21	14%
Renal and urinary disorders	47	31%	49	32%	8	5%	9	6%
Investigations	39	26%	43	29%	24	16%	20	13%
Eye disorders	37	24%	27	18%	2	1%	-	-
Hepatobiliary disorders	10	7%	7	5%	2	1%	2	1%
Ear and labyrinth disorders	9	6%	6	4%	1	0.7%	-	-
Reproductive system and breast disorders	8	5%	9	6%	-	-	1	0.7%
Endocrine disorders	4	3%	2	1%	1	0.7%	-	-
Immune system disorders	4	3%	3	2%	1	0.7%	0	0.7%

Source: FDA reviewer

The most common adverse reactions (≥20%) on the CPX-351 arm on Study 301 included hemorrhagic events, febrile neutropenia, edema, rash, nausea, mucositis, diarrhea/colitis, constipation, musculoskeletal pain, fatigue, dyspnea, abdominal pain , headache, cough, decreased appetite, pneumonia (excluding fungal pneumonias), arrhythmias, bacteremias (excluding sepsis), chills, sleep disorders, vomiting, non-conduction cardiotoxicities, dizziness, hypotension, pyrexia and hypoxia. Table 45 below depicts the rates of toxicities by preferred term of any grade that occurred at any point during CPX-351 or control treatment in at least 10% of patients on the CPX-351 arm, or of grade 3-5 that occurred at a rate of at least 5% in the CPX-351 arm.

Table 45: TEAE Within 30 Days of Last Dose, Any Cycle, Study 301, by PT

	All grades				Grades 3-5			
	CPX		7+3		CPX		7+3	
PT[a]	N=153		N=151		N=153		N=151	
Hemorrhage	113	74%	80	53%	18	12%	12	8%
Febrile neutropenia	107	70%	108	72%	104	68%	107	71%
Rash	84	55%	55	36%	8	5%	3	2%
Edema	82	55%	95	63%	1	0.7%	5	3%
Nausea	74	48%	81	54%	1	1%	1	1%
Mucositis	72	47%	74	49%	2	1%	8	5%
Diarrhea/colitis	71	46%	103	68%	4	3%	11	7%
Constipation	65	42%	59	39%	1	1%	0	0%
Musculoskeletal pain	62	41%	56	37%	5	3%	4	3%
Fatigue	58	38%	62	41%	9	6%	9	6%
Dyspnea	54	35%	55	36%	22	14%	18	12%
Abdominal pain	54	35%	48	32%	4	3%	4	3%
Headache	53	35%	38	25%	3	2%	1	1%
Cough	51	33%	35	23%	0	0%	1	1%
Decreased appetite	48	31%	60	40%	3	2%	5	3%
Pneumonia (except fungal)	47	31%	38	25%	37	24%	29	19%
Arrhythmia	47	31%	45	30%	10	7%	10	7%
Bacteremia (except sepsis)	42	27%	41	27%	39	25%	35	23%
Chills	41	27%	41	27%	0	0%	0	0%
Sleep disorders	39	25%	44	29%	2	1%	1	1%
Vomiting	39	25%	33	22%	1	1%	0	0%
Cardiotoxicity (myocardial)	36	24%	35	23%	17	11%	19	13%
Dizziness	35	23%	32	21%	2	1%	0	0%
Hypotension	34	22%	33	22%	9	6%	1	1%
Pyrexia	33	22%	25	17%	1	1%	2	1%
Hypoxia	30	20%	32	21%	20	13%	23	15%
Chest pain	30	20%	25	17%	6	4%	1	1%
Hypertension	30	20%	25	17%	17	11%	8	5%
Upper respiratory infection (except fungal)	30	20%	24	16%	4	3%	1	1%
Fungal infection	28	18%	21	14%	12	8%	9	6%
Delirium	25	16%	36	24%	4	3%	11	7%
Pleural effusion	25	16%	28	19%	3	2%	3	2%
Pruritus	25	16%	14	9%	0	0%	0	0%
Catheter/device/injection site reaction	24	16%	17	11%	0	0%	0	0%
Anxiety	22	14%	19	13%	0	0%	0	0%
Sepsis (except fungal)	21	14%	23	15%	20	13%	21	14%
Petechiae	21	14%	18	12%	0	0%	0	0%
Visual impairment (except bleeding)	19	12%	8	5%	1	1%	0	0%
Hemorrhoids	18	12%	12	8%	0	0%	0	0%
Renal insufficiency	17	11%	20	13%	7	5%	8	5%
Transfusion reaction	16	10%	14	9%	3	2%	1	1%
Thrombosis	15	10%	15	10%	4	3%	7	5%
Renal insufficiency	17	11%	20	13%	7	5%	8	5%

	All grades				Grades 3-5			
	CPX		7+3		CPX		7+3	
PT[a]	N=153		N=151		N=153		N=151	
Cellulitis	14	9%	13	9%	9	6%	5	3%
Clostiridial infection	12	8%	12	8%	7	5%	6	4%

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5)

TEAEs that occurred in ≥10% of the CPX-351 arm and at a ≥ 3% higher rate on the CPX-351 arm as compared to the 7+3 arm included haemorrhagic events (21% higher in the CPX-351 arm), rash (19%), cough (10%), headache (10%), visual impairment (7%), pruritis (7%), pneumonia (6%), pyrexia (5%), catheter/device/injection site reactions, fungal infections, haemorrhoids, URTIs, vomiting, abdominal pain (4% each), musculoskeletal pain, constipation, hypertension, and chest pain (3%) each. Other relevant terms that occurred at a ≥3% higher rate on the CPX-351 arm as compared to the 7+3 arm but at a rate <10% on the CPX-351 arm included presyncope (5% vs 0), abscess (5% vs 1%), night sweats (9% vs 5%) and lymphadenopathy (3%).

It is notable that for the GI toxicities of nausea and diarrhea, known side effects associated with 7+3 therapy, patients treated with CPX-351 experienced these toxicities at lower rates compared to the 7+3 control (48% vs 54% and 46% vs 68%, in the CPX-351 and control arms, respectively).

Overall, in study 301 more patients on the CPX-351 arm completed 2 cycles of consolidation as compared to the control arm (See Table 35). Consequently, a comparative analysis of all TEAEs in each arm could potentially overestimate the toxicity of treatment with CPX-351 when in fact the differences might be due to differences in exposure. To explore this possibility and allow for a more equitable comparison, FDA performed an analysis of TEAEs in induction by arm, and in each cycle of consolidation by arm. The results are depicted in Table 46 below.

Induction Cycle(s):

Table 46: TEAEs Occuring at a Rate of 10% or Greater in the CPX-351 Arm During Either Induction Cycle, Study 301

	All grades		Grade ≥ 3	
	CPX-351	7+3	CPX-351	7+3
PT[a]	N=153	N=151	N=153	N=151
Hemorrhage broad	107 (70)	74 (49)	15 (10)	9 (6)
Febrile neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash	82 (54)	55 (36)	8 (5)	2 (1)
Edema	78 (51)	90 (59)	2 (1)	5 (3)
Nausea	72 (47)	79 (52)	1 (0.7)	1 (0.7)
Diarrhea/colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)

	All grades		Grade ≥ 3	
PT[a]	CPX-351 N=153	7+3 N=151	CPX-351 N=153	7+3 N=151
Constipation	61 (40)	57 (38)		-
Musculoskeletal pain	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain	51 (33)	45 (30)	3 (2)	3 (2)
Headache	51 (33)	36 (24)	3 (2)	3 (2)
Cough	51 (33)	34 (23)	-	1 (0.7)
Fatigue	49 (32)	58 (38)	8 (5)	8 (5)
Dyspnea	49 (32)	51 (34)	17 (11)	15 (10)
Arrhythmia	46 (30)	41 (27)	10 (7)	7 (5)
Decreased appetite	44 (29)	57 (38)	2 (1)	5 (3)
Pneumonia (except fungal)	39 (26)	35 (23)	30 (20)	26 (17)
Sleep disorders	38 (25)	42 (28)	2 (1)	1 (0.7)
Bacteremia (except fungal)	37 (24)	37 (24)	35 (23)	31 (21)
Vomiting	37 (24)	33 (22)		-
Chills	35 (23)	38 (25)		-
Cardiotoxicity (myocardial)	31 (20)	27 (18)	13 (9)	15 (10)
Hypotension	30 (20)	32 (21)	7 (5)	1 (0.7)
Hypoxia	28(18)	31 (21)	19 (12)	23 (15)
Hypertension	28 (18)	22 (15)	15 (10)	8 (5)
URTI (except fungal)	28 (18)	19 (13)	4 (3)	1 (0.7)
Dizziness	27 (18)	26 (17)	1 (0.7)	-
Fungal infection	27 (18)	19 (13)	11 (7)	9 (6)
Pyrexia	26 (17)	23 (15)	1 (0.7)	2 (1)
Chest pain	26 (17)	22 (15)	5 (3)	-
Delirium	24 (16)	33 (22)	4 (3)	9 (6)
Pleural effusion	24 (16)	25 (17)	3 (2)	2 (1)
Catheter-device-injection site reaction	24 (16)	15 (10)		-
Pruritus	23 (15)	14 (9)		-
Anxiety	21 (14)	16 (11)		-
Sepsis except fungal	17 (11)	20 (13)		*n/a**
Petechiae	17 (11)	17 (11)		-
Transfusion reaction	16 (11)	16 (11)	3 (2)	1 (0.7)
Hemorrhoids	16 (11)	12 (8)		-
Visual impairment (except bleeding)	16 (11)	8 (5)		-
Renal insufficiency	17 (11)	17 (11)	7 (5)	7 (5)
Clostridial infection (except sepsis or bacteremia)	12 (8)	12 (8)	7 (5)	5 (3)

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5); n/a: not applicable; *in the ADAE dataset, grade 3 or greater events in the sepsis category were coded for only 16 (10%) on the CPX-351 arm and 18 (12%) on the control arm. However, since according to CTCAE grading, sepsis is by definition grade 3, the table does not depict a difference between sepsis events of different grades in this table.

Although the rate of mucositis, a known toxicity associated with 7+3 therapy, was about the same in both arms, it is relevant that grade 3-5 mucositis occurred in <2 % of patients, compared to 5% in the control arm. The same trend is seen for decreased appetite, often related to mucositis.

The reason for an increased rate of visual impairment on the CPX-351 arm is not readily apparent. All PTs in this category where of grade 1-2, and they included, in order of decreasing frequency: vision blurred, visual impairment, vitreous floaters, photophobia, uveitis, photopsia and retinal tear. Although the rates were lower in the control arm, the terms were similar: vision blurred, scintillating scotoma, photophobia, vitreous floaters, visual impairment, vitreous detachment, and photopsia. Throughout the treatment period, there was 1 grade 3 TEAE of visual acuity reduced, in one eye. As noted above (section 7.4.3), the narratives included in the submission did not contain adequate information to tease apart this category of toxicity further. In response to an Agency IR requesting more information regarding these toxicities, the applicant provided slightly more detail. According to the applicant, no dose changes were made due to these events; the patient with the grade 3 toxicity noted above had concurrent giant cell arteritis and received steroids. However, it is noted that this patient had reason for treatment discontinuation adjudicated by FDA, and assessed that it was this toxicity that led to treatment discontinuation in this patient. The event recovered "with sequelae" but no further details are provided. One other case of grade 1 vision blurred is reported to have recovered with sequelae as well; the remainder of the events in this category are reported as recovered/resolved, with the caveat as to the reliability of the outcome in the ADAE dataset as described in section 7.4.3 above.

This trend of increased rates of visual impairment with CPX-351 treatment was consistent in the pooled safety population as well, as it occurred in 42 of the 365 patients who received the 100 units/m^2 dose of CPX-351 (12%), quite similar to that seen during induction in Study 301. Across the safety population, 1 patient had grade 4 blindness, which resolved ((b) (6)); notably, this occurred concurrently with disseminated fungal infection including fungal retinitis such that it appears not to be a neurologic adverse reaction of CPX-351 treatment at its root cause. The only grade 3 event in this category was the one on Study 301 detailed above; the remainder of the events in this category in the pooled safety database were grades 1-2 and resolved without interruption or discontinuation of therapy.

Reviewer comment: At the time of this review, the Agency received a response to an IR by the CMC review team regarding the heavy metal impurities detected in the drug product vials. In this response, the levels for (b) (4) ***were not included; they were still under investigation due to results that were higher than expected (reportedly 6 times the permitted daily exposure (PDE) for*** (b) (4) ***The retest data showed that the*** (b) (4) ***levels were below the PDE, although the commercial batches have greater levels of*** (b) (4) ***than the clinical batches. See CMC review for full details. Neurologic toxicities in general, and visual disturbances including those described above in Study 301 and the ISS, are known toxicities associated with elevated*** (b) (4) ***levels, for example optic nerve atrophy, reduced visual acuity, blindness, retinal***

dysfunction, poor color vision, blurred vision (b) (4) All of these were seen on study 301 or in the pooled safety population. It is noted that most of these (b) (4) toxicities are reversible upon cessation of exposure, consistent with the findings on the studies. Since (b) (4) levels were not measured in patients across the CPX-351 clinical development program, the association between these toxicities and increased (b) (4) levels remains uncertain. Overall, these findings do not alter the risk: benefit assessment of CPX-351 therapy. However, given the clinical data in the context of the impurity findings, the warning and precaution for Wilson's disease should be a broader one for heavy metal toxicity as well.

Other notable adverse reactions occurring during induction cycle 1 or 2 in less than 10% of patients treated with CPX-351 included the following:

- Dyspepsia occurred in 13 patients (9%) on the CPX-351 arm, compared with 9 patients (6%) on the control arm. Since the rate of mucositis was the same in both arms (44%), the significance of this finding is unclear.

- Phlebitis, which occurred in 8 patients (5%) in the CPX-351 arm compared to 3 (2%) in the control arm. However, since most of the events occurred >10 days after the last dose of study drug, the relation to CPX-351 is unlikely.

- The following non-laboratory TEAEs occurred ≥3% more frequently on the CPX-351 arm compared with the control arm:

    - Presyncope (4% vs 0)
    - Night sweats (9% vs 5%)
    - Abscess (5% vs 1%)
    - Hearing impaired: 2% vs 0
    - Eye irritation: 8% vs 6%; eye irritat48ion is a known toxicity of cytarabine, one of the components of CPX-351

Consolidation Cycle 1:

Notable TEAEs occurring at a frequency of greater than 10% in the CPX-351 arm during the first consolidation cycle are detailed in Table 47 below. TEAEs during this cycle occurring in more than one patient but at a frequency of <10% in the CPX-351 arm, and at a frequency of greater than 2% in the CPX-351 arm compared to the control arm were observed in

- Cellulitis: 3 (6%) vs 1 (3%)
- Hypotension: 3 (6%) vs 1 (3%)
- Visual impairment (excluding bleeding): 2 (4%) vs 0
- Vomiting: 3 (6%) vs 1 (3%)

Table 47: TEAEs that Occurred at a Frequency of 10% or Greater in the CPX-351 Arm During Consolidation cycle 1, Study 301

	All grades		Grade ≥3	
PT[a]	CPX-351 N=49	7+3 N=32	CPX-351 N=49	7+3 N=32
Hemorrhage broad	15 (31)	5 (16)	1 (2)	1 (3)
Febrile neutropenia	10 (20)	5 (16)	10 (20)	5 (16)
Nausea	8 (16)	3 (9)	-	
Constipation	7 (14)	7 (22)	1 (2)	-
Fatigue	6 (12)	9 (28)	1 (2)	-
Mucositis	6 (12)	5 (16)	-	1 (3)
Musculoskeletal pain	6 (12)	1 (3)	-	
Pyrexia	6 (12)	2 (6)	-	
Edema	5 (10)	9 (28)	-	
Abdominal pain	5 (10)	7 (22)	1 (2)	1 (3)

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5)

The only grade ≥3 TEAE that occurred at a frequency of 5% or greater on the CPX-351 arm and at an overall rate of <10% on that arm during Consolidation Cycle 1 was cellulitis, which occurred in 6% of patients on the CPX-351 arm and 3% on the control arm.

There was no myocardial cardiotoxicity in the CPX-351 on the CPX-351 arm during consolidation 1, compared to 4 patients (13%) who experienced this toxicity in the control arm, 2 (6%) at grade 3 or higher. The trends with regard to TEAEs during consolidation roughly mirrored those seen during induction, with the exception of rash, which occurred in fewer patients (8%) on the CPX-351 arm compared to 10% on the control arm.

Only 23 patients in the CPX-351 arm and 11 patients in the 7+3 arm received a second cycle of consolidation, and these small numbers make interpretation difficult. The rates of TEAEs that occurred at a frequency of 10% or greater on the CPX-351 arm are depicted in Table 48 below:

Table 48: TEAEs that Occurred at a Rate of 10% or Greater, or grade >3 at 5% or Greater, in the CPX-351 Arm During Consolidation cycle 2, Study 301

	All grades		Grade ≥3	
PT[a]	CPX-351 N=23	7+3 N=11	CPX-351 N=23	7+3 N=11
Hemorrhage broad	8 (35)	1 (9)	2 (9)	-
Fatigue	7 (30)	2 (18)	2 (9)	1 (9)
Chills	7 (30)	1 (9)	-	
Edema	6 (26)	4 (36)	-	
Febrile neutropenia	6 (26)	3 (27)	6 (26)	3 (27)

	All grades		Grade ≥ 3	
PT[a]	CPX-351 N=23	7+3 N=11	CPX-351 N=23	7+3 N=11
Constipation	5 (22)	3 (27)		-
Dizziness	5 (22)	-		-
Mucositis	4 (17)	3 (27)		-
Decreased appetite	4)17)	1 (9)	1 (4)	-
Musculoskeletal pain	4 (17)	-		-
Nausea	3 (13)	5 (45)		-
Arrhythmia	3 (13)	3 (27)	-	2 (18)
Rash	3 (13)	2 (18)	-	1 (10)
Dyspnea	3 (13)	-	2 (9)	-
Petechiae	3 (13)	-		-
Pneumonia (except fungal)	2 (9)	1 (9)	2 (9)	1 (9)
Syncope	2 (9)	-	2 (9)	-

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5)

Two patients in the CPX-351 arm experienced myocardial cardiotoxicity, 1 at grade 3, and no patients in the control arm experienced this type of toxicity during cycle 2 of consolidation.

FDA performed an exploratory analysis of TEAEs in the pooled safety database to detect signals of toxicities that were not manifest in Study 301. The results are detailed in Table 49 below; no significant differences in safety profile for CPX-351 was detected during this analysis.

Table 49: TEAE at CPX-351 100 units/m2, Pooled Safety Population

	All Grades		Grades 3-5 %	
PT[a]	N=365			
Hemorrhage	245	67%	47	13%
Febrile neutropenia	235	64%	231	63%
Rash	226	62%	28	8%
Nausea	199	55%	6	2%
Edema	199	55%	10	3%
Mucositis	189	52%	9	2%
Diarrhea/colitis	183	50%	22	6%
Fatigue	170	47%	37	10%
Musculoskeletal pain	165	45%	19	5%
Constipation	161	44%	4	1%
Dyspnea	135	37%	49	13%
Abdominal pain	132	36%	11	3%
Decreased appetite	128	35%	7	2%
Headache	128	35%	4	1%
Cough	126	35%	0	0%
Chills	112	31%	1	0%
Arrhythmia	112	30%	16	4%
Vomiting	111	30%	1	0%

PT[a]	All Grades N=365		Grades 3-5 % N=365	
Pyrexia	109	30%	11	3%
Pneumonia (excluding fungal)	96	26%	74	20%
Sepsis (excluding fungal)	94	26%	89	24%
Sleep disorder	92	25%	2	1%
Non-conduction cardiotoxicity	86	24%	29	8%
Dizziness	84	23%	3	1%
Hypotension	82	22%	17	5%
Catheter/device/injection site reaction	81	22%	0	0%
Bacteremia (excluding sepsis)	78	21%	69	19%
URTI (excluding fungal)	72	20%	6	2%
Fungal infection	70	19%	34	9%
Pruritus	70	19%	0	0%
Petechiae	67	18%	2	1%
Anxiety	65	18%	0	0%
Chest pain	64	18%	7	2%
Hypoxia	64	18%	37	10%
Hypertension	63	17%	25	7%
Delirium	57	16%	9	2%
Pleural effusion	57	16%	4	1%
Hypokalemia	48	13%	22	6%
Depression	43	12%	0	0%
Renal insufficiency	43	12%	22	6%
Transfusion reaction	42	12%	7	2%
Visual impairment (except bleeding)	42	12%	2	1%
Hyperhidrosis	39	11%	1	0%
Thrombosis	38	10%	7	2%
Altered state of consciousness	37	10%	11	3%
Cellulitis	36	10%	17	5%
Dyspepsia	36	10%	2	1%
Peripheral neuropathy	35	10%	2	1%

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5); URTI, upper respiratory tract infection

Laboratory Findings

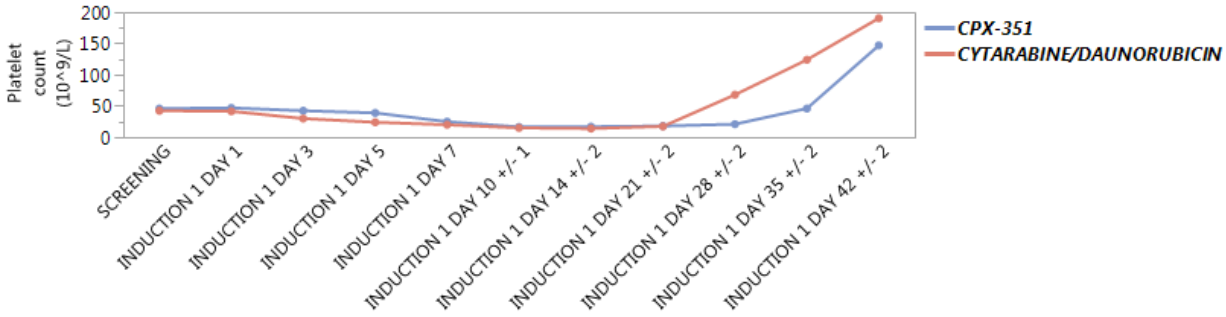
Hematologic parameters:

An expected pharmacodynamic effect of any intensive treatment for AML, and specifically the APIs of CPX-351, cytarabine and daunorubicin, is myelosuppression and consequent anemia, thrombocytopenia and neutropenia. Thrombocytopenia and neutropenia put patients at risk for bleeding and infections, respectively, and the increased incidences of these AEs in CPX-351 treated subjects was discussed in detail above. An analysis of platelets and neutrophils in subjects on study 301 is consistent with these findings.

Thrombocytopenia
Although median platelet counts returned to the ≥50,000/mcL range for both arms by about day 35 of induction 1, the duration of severe thrombocytopenia was longer for patients in the CPX-351 arm than for those in the control arm. In induction 1, both arms achieved a median

platelet nadir and remained there through day 21 (median platelet count of 18,000/mcL for each arm); but whereas the CPX-351 arm remained at that nadir with only a slight median increase at day 28 (21,000/mcL), returning only to 46,000/mcL at day 35, the 7+3 arm had increased to a median of 68,000/mcL by day 28 and was over 100,000/mcL by day 35 (See Figure 21 below).

Figure 21: Median Platelet Counts, Induction 1, Study 301

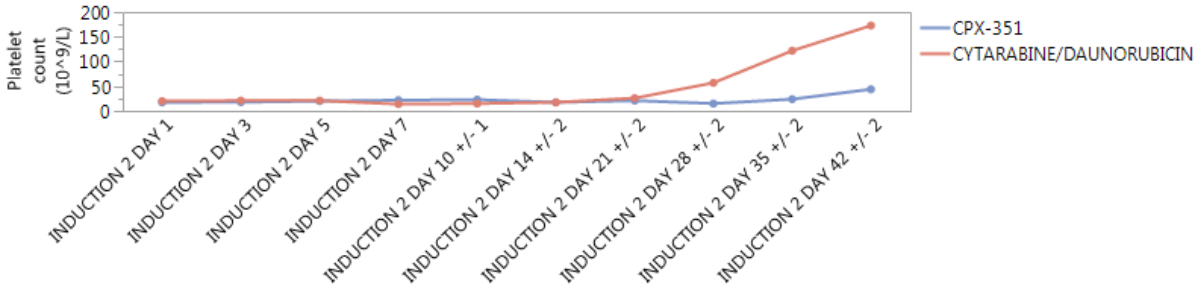


Median time to platelet receovery to ≥50,000/mcL after induction 1 was 35 days (range 7-106) in the CPX-351 arm and 29 days (range 10-144) in the control arm.

The applicant analyzed delayed platelet recovery in patients without evidence of progressive disease (CR+CRi per applicant) during induction 1; in this analysis, 16 /58 patients (28%) on the CPX-351 arm had recovery of platelets to >50,000/mcL later than day 42, compared to 4/34 (12%) in the control arm. For consolidation 1, 12/48 (25%) of patients in CR or CRi on the CPX-351 arm had delayed platelet recovery, compared to 5/32 (16%) on the control arm.

The delayed platelet recovery in the CPX-351 arm was more pronounced during induction 2, where the median platelet counts in the control arm were less than grade 3 by day 28 (57,000/mcL), whereas those for the CPX-351 arm did not achieve this even by day 42 (44,000/mcL).

Figure 22: Median Platelet Counts, Induction 2, Study 301



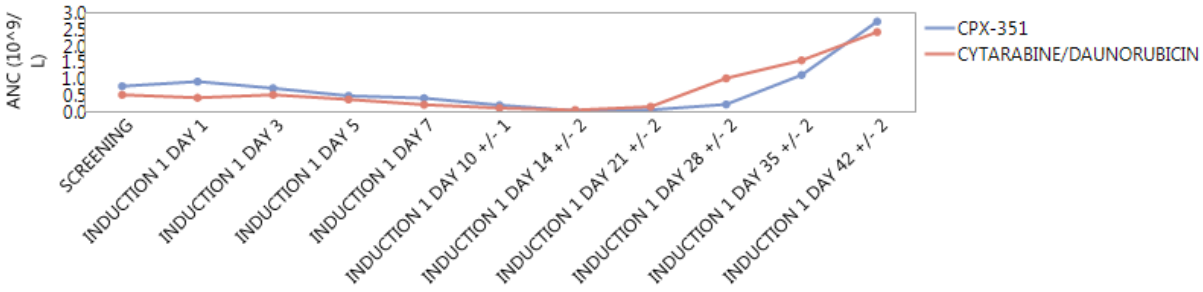
Reviewer comment: the prolonged thrombocytopenia in the CPX-351 arm as compared with 7+3, coupled with increased hemorrhagic events, including fatal events, as described above

(Table 40) warrants a warning and precaution in the label for these events.

Neutropenia

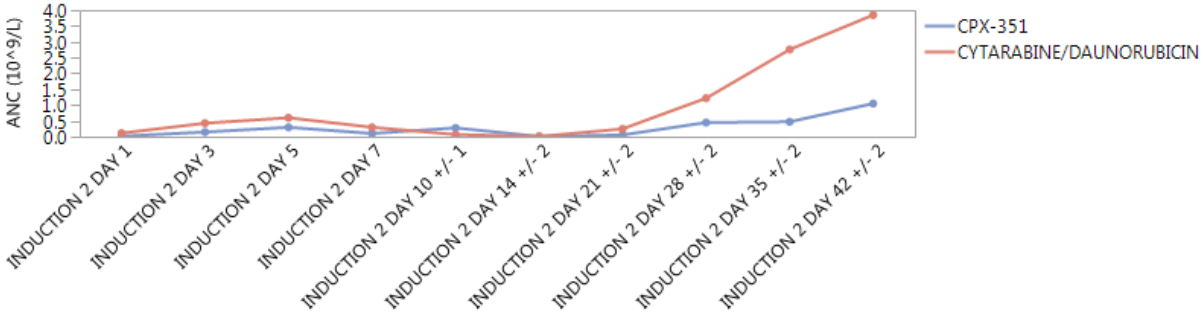
For neutrophil recovery, the differences between the arms during induction 1 were not reflected in a longer median time to ANC recovery to ≥ 500/mcL , which were similar in both arms: 29 days (range 7-96) in the CPX-351 arm versus 31 days (range 10-57) in the control arm. Notably, when looking at the median ANC in each arm at the 28 day timepoint, it is lower in the CPX-351 arm (210) compared to 1000 in the control arm (Figure 23):

Figure 23: Median ANC, Induction 1, Study 301



Similar to the trend in platelet recovery, the difference between the arms with regard to neutrophil recovery was more pronounced after induction 2; median time to ANC recovery to 500/mcL in the CPX-351 arm was 35 days (range 5-78) compared to 28 days (range 7-36) in the control arm. Patients treated with CPX-351 had a median ANC that was still in the grade 4 neutropenia range (450) on day 28, as compared to patients in the control arm for whom the median ANC had crossed the grade 2 threshold (1220) by day 28.

Figure 24: Median ANC, Induction 2, Study 301



The applicant performed an analysis of prolonged neutrophil recovery (recovery to ANC of 500/mcL after day 42) for patients without evidence progressive leukemia during induction 1 and consolidation 1, similar to that done for platelets above. On the CPX-351 arm, 10/58

patients (17%) had ANC recovery to this level after day 42 of induction 1, compared to 1/34 (3%) on the control arm. During consolidation 1, 5/48 patients (10%) without evidence of progressive disease on the CPX-351 arm had delayed ANC recovery, compared to 1/32 patients (3%) on the control arm.

Chemistries

All patients in both arms had at least a grade 1 laboratory toxicity at any point on study 301. Grade 3-4 laboratory toxicities by arm are summarized in Table 50 below, and includes any abnormality that occurred in ≥5% of patients on the CPX-351 arm; no laboratory toxicities grades 3-5 not listed below occurred more frequently on the CPX-351 arm than on the control arm.

Table 50: Grade >2 Treatment Emergent Laboratory Toxicities, Study 301, All Cycles

	CPX-351 N=153		7+3 N=151	
Hyponatremia	24	16%	22	15%
Hyperglycemia	18	12%	27	18%
Hypokalemia	16	10%	24	16%
Hypoalbuminemia	12	8%	24	16%
Hyperbilirubinemia	9	6%	9	6%
Elevated ALT	8	5%	9	6%

FDA reviewer analysis

Due to the differences in exposure between the arms discussed above, FDA performed an analysis of laboratory TEAEs >grade 2 limited to induction. On this analysis, only hyponatremia, hypokalemia, hypoalbuminemia and hyperbilirubinemia occurred at a rate of >5% on the CPX-351 arm.

Table 51: Grade >2 Treatment Emergent Laboratory Toxicities, Study 301, Induction Only

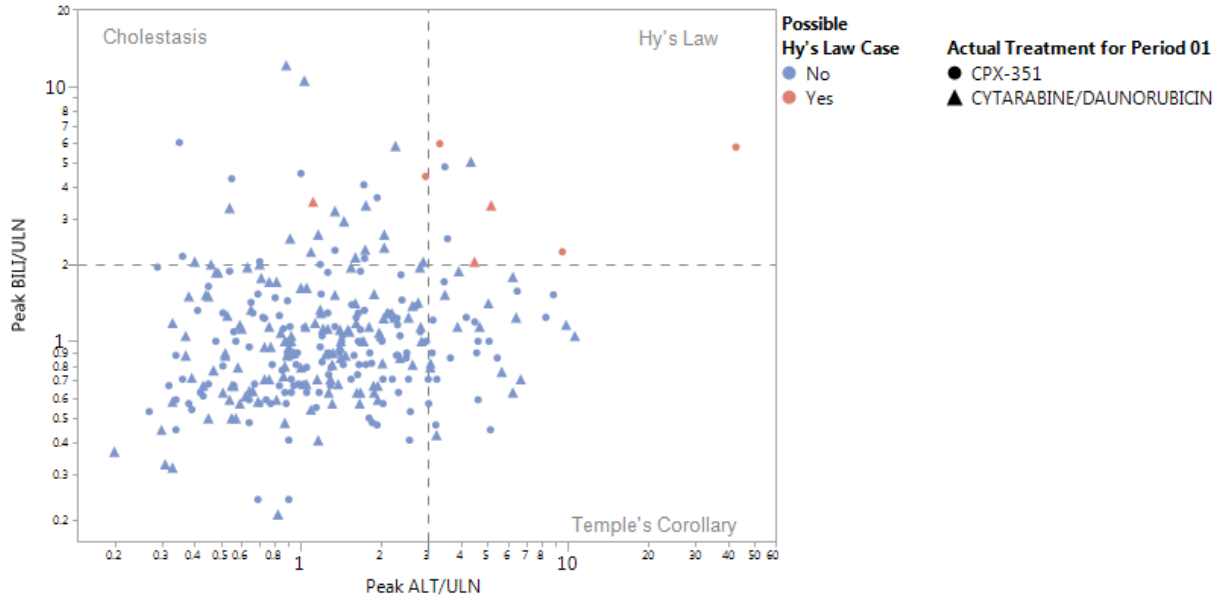
	CPX-351 N=153		7+3 N=151	
Hyponatremia	21	14%	20	13%
Hypokalemia	14	9%	19	13%
Hypoalbuminemia	11	7%	20	13%
Hyperbilirubinemia	9	6%	6	4%

FDA Reviewer Analysis

Potential Hy's law cases

As depicted in Table 48 and Table 49 above, the rate of hepatotoxicity was not higher in the CPX-351 arm compared to the control arm, and only graade 3-4 hyperebilirubinemia happened

at a rate of >5% , at 6%. FDA identified 3 potential Hy's law cases on the CPX-351 arm, and 2 on the control arm, as depicted below:



Source: FDA reviewer analysis (JMP Clinical 6)

All patients had confounding factors contributing to hepatotoxicity, including: in 1 patient ((b) (6)), this coincided with an episode of sepsis during induction and resolved. In 1 patient ((b) (6)), it coincided with a siezure, MI and bacteremia during induction 2. In the 3rd patient ((b) (6)), it occurred during a case of pneumonia, hypotension and decreasing performance status in a patient receiving multiple concomitant medications.

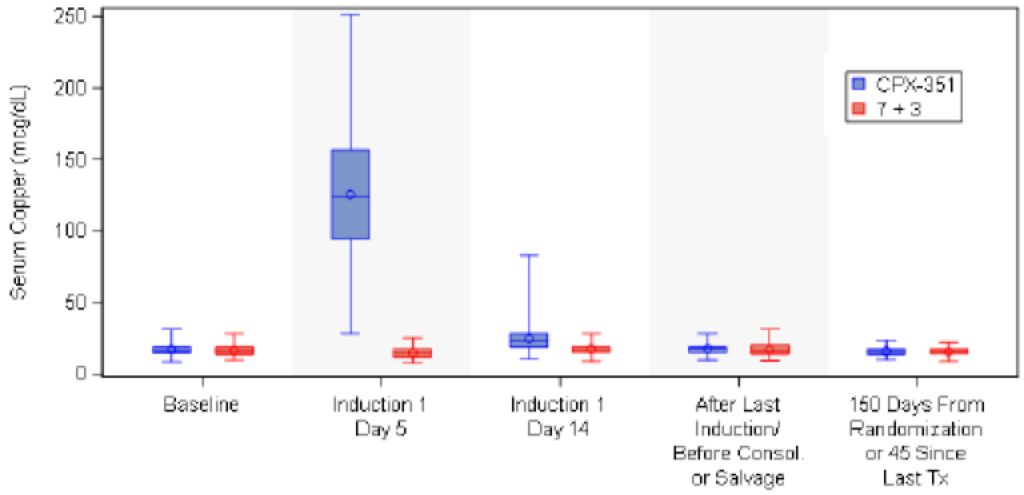
Reviewer comment: No signal for DILI was associated with CPX-351 therapy.

Copper Levels

CPX-351 contains 5 mg/mL copper gluconate, of which 14% is elemental copper. In a typical patient (BSA 1.7 m^2), the maximum exposure of copper per dose of CPX-351 is 24 mg, and the maximum theoretical total exposure of copper under the proposed dosing regimen is (b) (4) (see section 5 for details). One of the secondary objectives of Study 301 was to assess serum copper elevations in treated patients, and the applicant assessed serum copper levels on study 301 at baseline and on days 5 (10 minutes after completion of the day 5 infusion), 14, after the last induction dose and at day 150. Patients in whom serum copper levels were elevated (>20% above the ULN) at day 150 continued to be followed monthly until 1 year from randomization or documentation of return of serum copper to normal levels.

The Applicant performed an analysis of serum copper levels by treatment arm, as depicted in Figure 25 below:

Figure 25: Serum Copper Concentrations by Arm and Visit, Study 301



Source: Applicant Clinical Study Report, Section 12.3.4, page 83

The Applicant described that subjects treated with CPX-351 had elevated copper concentrations at day 5 following Induction 1, which were not seen in the control arm. However, they returned to baseline in 87% of patients in the CPX-351 arm by day 14 and all patients by day 150 after final treatment (in patients who survived and had a measurement for copper concentration). The applicant's CSR (9.5.4.6) stated that "*Subjects with persistently elevated coper concentrations were evaluated for clinical abnormalities associated with copper toxicity;*" the protocol background (16.1.1, version 2.3, November 4, 2013, section 2.6.4, page 266) noted that no copper-attributable toxicities were seen in animal studies, and that the datat from the clinical studies were consistent with the preclinical findings. In response to an Agency IR (b) (4) (see Prescribing Information section 10.1), they stated that their analysis of copper levels depicted above, together with results from the PK study (Study 206), where the concentration-time curves for cytarabine, daunorubicin and copper following CPX-351 administration were parallel, "*suggest high retention of copper within the CPX-351 liposomes, where it is not biovalaible…copper is likely to be very slowly released from CPX-351 liposomes in vivo.*" They thus conclude that the burden to excretory organs is expected to be very low.

Reviewer comment: This conclusion regarding slow release of copper form the liposomes appears to be inconsistent with the relatively rapid increase in serum copper levels on day 5 as depicted in the figure above.

FDA noted that this analysis was limited by the fact that only 90 patients on day 14, 77 patients after last induction and 63 patients on day 150 had copper levels at each timepoint. Also, the FDA performed a detailed analysis of TEAEs in the SOCs for Nervous System or Psychiatric Disorders, as these are known manifestations of copper toxicity in patients with Wilson's Disease (Bostantjopoulou et al 2017). See section 7.5.4 for details regarding this analysis.

Vital Signs

The schedule of safety evaluations for each protocol was described in Section 7.2.1above. The frequency of monitoring was considered adequate, with the exception of vital signs. In the phase 1 dose finding study (101, see section7.4.7 for details), vital signs were only measured daily, such that the detection of infusion related reactions (IRRs) could have been missed. In subsequent studies, monitoring of vital signs was even less frequent, required only on days 14 and 42 of studies 204, 205 and 301.

For both Study 301 and the pooled safety population, the applicant provided summaries of the baseline vital signs that included mean, median, and range measurements of blood pressure, pulse, respiratory rate and temperature; for the pooled safety population they provided absolute measurements on days 14 and 42 of both induction and consolidation cycles by arm, and for Study 301 they presented an additional analysis of changes from baseline. They concluded that "vital signs were stable in both treatment groups and no clinically significant differences were observed between the CPX-351 and 7+3 treatment groups" (CSR for 301, section 12.4.1, and Table 14.3.5.1). FDA repeated these analyses for study 301 and the results were consistent with the applicant's findings (Figure 26, Figure 27, Figure 28, and Figure 29 below). However, the limited time points at which VS were recorded limit the interpretation of these analyses.

Figure 26: Mean SBP Over Time, Study 301

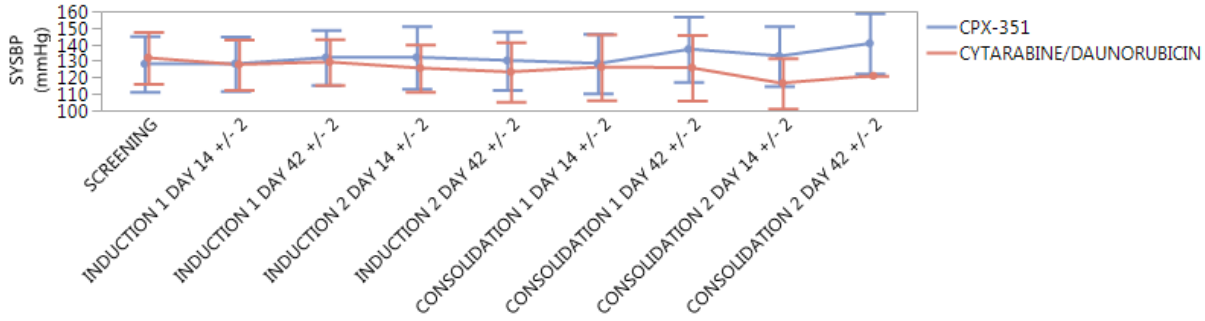


Figure 27: Mean RR Over Time, Study 301

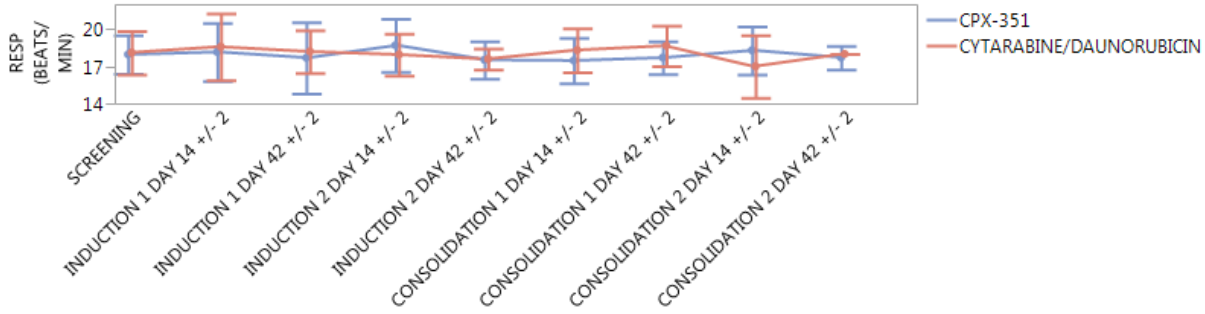


Figure 28: Mean Temperature Over Time, Study 301

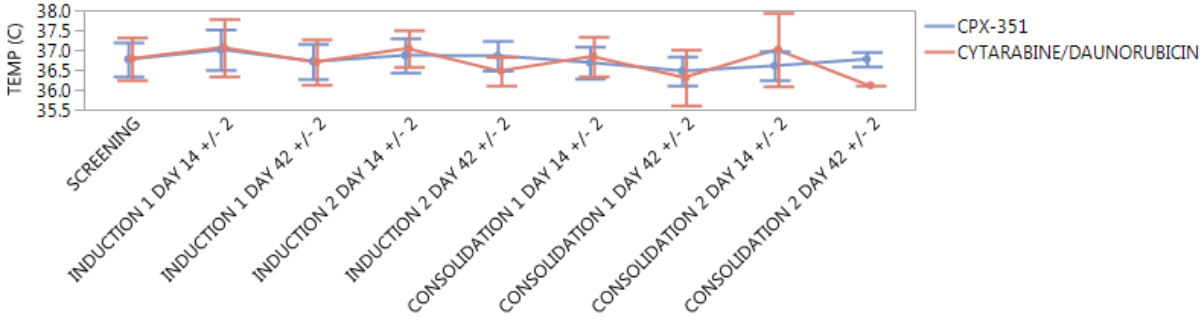
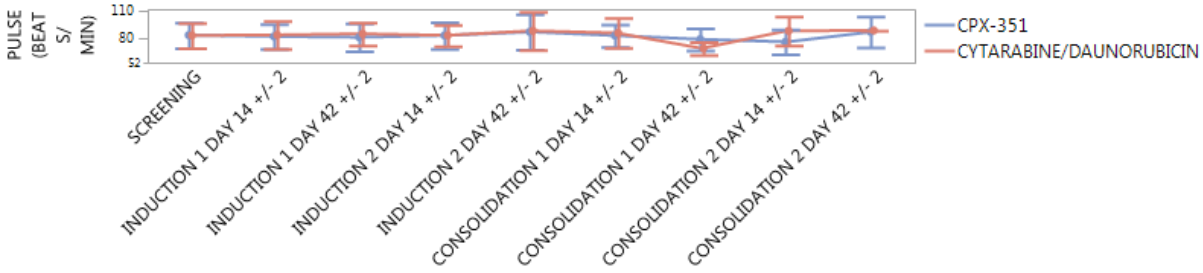


Figure 29: Mean Pulse Over Time, Study 301



Source: FDA reviewer analysis

Reviewer comment: Given the lack of frequent vital sign assessment on the day of CPX-351 infusion throughout the development plan, together with the safety findings that could be representative of infusion reactions (e.g. grade 3 hypotension that occurred at a rate of 6% in the CPX-351 arm vs 0.7% in the control arm), a PMR to assess the incidence of these reactions with CPX-351 is necessary to ensure that health care providers administering the product are aware of the signs, symptoms and timing of these reactions, if they occur, as well as to provide strategies for drug interruption and/or re-challenge for these events.

Electrocardiograms (ECGs)

The applicant analyzed the pooled safety database for ECG abnormalities. According to their analysis (ISS section 4.2, page 116), half of the CPX-351 treated patients had abnormal ECGs at baseline, and 52% of those treated with any salvage regimen (including 54% of those treated with 7+3) had abnormal ECGs at baseline. At the last observation, 59% of patients treated with CPX-351 and 74% of the controls (80% of those who received 7+3) had abnormal ECGs. They thus conclude that "*When ECG data were summarized for the Pooled Safety population, the incidence of normal and abnormal ECGs was similar between the CPX-351 treatment group and All Controls*." It is noted that on Study 301, ECGs were performed only at baseline, day 150 (or 45 days after the last treatment), and at early trial termination, on Study 204 they were done only at screening and trial termination, and on Study 101, they were done only prior to

treatment initiation. On Study 205, there were done on day 42 of the last induction and each consolidation cycle as well. It is thus difficult to make any definitive conclusions as to ECG changes with the exception of the QT study (See next paragraph). FDA analyzed the pooled safety database of patients who got CPX-351 at the proposed 100 units/m^2 dose. Analyses of arrhythmias and non-conduction cardiac toxicities are included in the previous section on TEAES. With regard specifically to ECG abnormalities in the SOC "Investigations," overall, 8 patients had ECG abnormalities, including 3 cases of QT prolongation, 1 each on studies 101, 205 and 301. The other ECG abnormalities included ST abnormalities (Study 101, 204) and t-wave abnormalities (Study 204, 205, 301). On Study 301, 32 patients on the control arm and 2 patients on the CPX-351 arm had ECG abnormalities; all 3 abnormalities on the control arm were QTc prolongation. On the CPX-351 arm, the abnormalities were T-wave abnormal and elevated QT.

QT

The Interdisciplinary Review Team for QT Studies (IRT) was consulted to review the application, specifically Study CLTR0310-206, the dedicated QT study. In this non-randomized, open label Phase 2 study, 26 patients with acute leukemia or MDS received CPX-351 at a dose of 100 units/m^2 on days 1, 3 and 5, over 90 minutes. While the applicant proposed language in labeling that stated that "(b) (4) ," the IRT assessed that Study 206 was not designed to exclude small mean QTc prolongation of 10 ms, such that the above language was not appropriate. Instead, they suggested language stating that "*At the therapeutic exposures with the recommended dosing regimen of VYXEOS, no large mean changes in the QTc interval (i.e., >20 ms) were detected in the study. An exposure-QTc analysis suggested no concentration-dependent QTc interval prolongation*." See full consult for details.

Immunogenicity

The product is a liposomal formulation of 2 cytotoxic drugs, such that immunogenicity is not a concern with this product.

7.4.5. Analysis of Submission-Specific Safety Issues

Cardiotoxicity

Cardiotoxicity is a known adverse reaction seen with daunorubicin, and to a lesser extent with cytarabine, the APIs contained in CPX-351. Across the development program, excluding the patients from study 204 who crossed over to CPX-351 treatment, 180 out of 393 patients (46%) treated with CPX-351 at any dose experienced a TEAE that was grouped into the broad cardiotoxicity category by FDA (see Table 62 for an exhaustive list of terms included in this category), as compared to 95 out of 226 patients (42%) on either the 7+3 or salvage control arms. In the CPX-351 treated patients, 45/393 (11%) experienced a TEAE in this category that was of grade 3 or greater, compared to 36/226 (16%) in those treated with any control. Grade 5

events in this category occurred in 2 patients treated with CPX-351 (cardiopulmonary arrest and cardiac arrest, both at the 100 units/m^2 dose that occurred on day 11 and 59 of study treatment, respectively). The case on day 59 occurred during the follow up period. Seven patients in any control arm experienced a Grade 5 event in this category, including cardiac arrest in 2 patients, cardiac failure in 2 patients, and atrial fibrillation, cardio-respiratory arrest and MI in 1 patient in 1 patient each; these occurred as early as day 10 and as late as day 112 of therapy, and all but 1 (cardio-respiratory arrest) occurred during induction or consolidation. Looking only at the patients treated with 100 units/m^2 of CPX-351 during induction, cardiotoxicity occurred in 170 patients (47%), and 40 of these were grade 3 or greater (11%). When compared to only the 167 patients who received 7+3 as control therapy (excluding crossovers from 204 as well as patients who received an alternative consolidation as per protocol), the incidence of cardiotoxicity was similar at 46% (77 patients), and the incidence of grade 3 or higher events in this category was more than twice that seen in the CPX-351 group (29/167 patients, 23%).

On trial 301, 68 patients (44%) of patients on the CPX-351 arm experienced treatment-emergent cardiotoxicity, as defined above, the same rate as on the control arm (67 patients). Of these, 22 patients on the CPX-arm (14%) experienced these events at grade $\geq$3, compared to 26 patients (17%) on the control arm.

Looking specifically at non-conduction, myocardial toxicity (see terms in13.5) on trial 301 (all cycles), 43 patients (28%) on each arm experienced this toxicity, including 20 patients (13%) on the CPX-351 arm and 23 patients (15%) who experienced an event that was grade $\geq$3. This included 1 death due to cardiac arrest on the CPX-351 arm and 2 deaths on the control arm, one due to cardiac arrest and one due to congestive heart failure.

Finally, looking exclusively at the grouped term cardiac failure (as defined in Table 62), across the development program, 23 patients (6%) on the CPX-351 arm experienced this TEAE, which was lower than the incidence on the control arm (19 patients, 8%). On trial 301, the trend was similar, with 10 patients (7%) experiencing cardiac failure in the CPX-351 arm compared with 13 patients (9%) on the control arm.

Reviewer comment: Any analysis of the ISS is subject to interpretation constraints related to the uncontrolled nature of the trials and heterogeneity among patient populations. However, these exploratory findings do provide support for those found in 301, and the consistency of the findings provide additional evidence that cardiotoxicity with CPX-351 does not appear to be greater than that seen with its APIs, both of which are used as part of SOC for the treatment of newly diagnosed AML. This supports the favorable benefit-risk assessment for CPX-351 therapy.

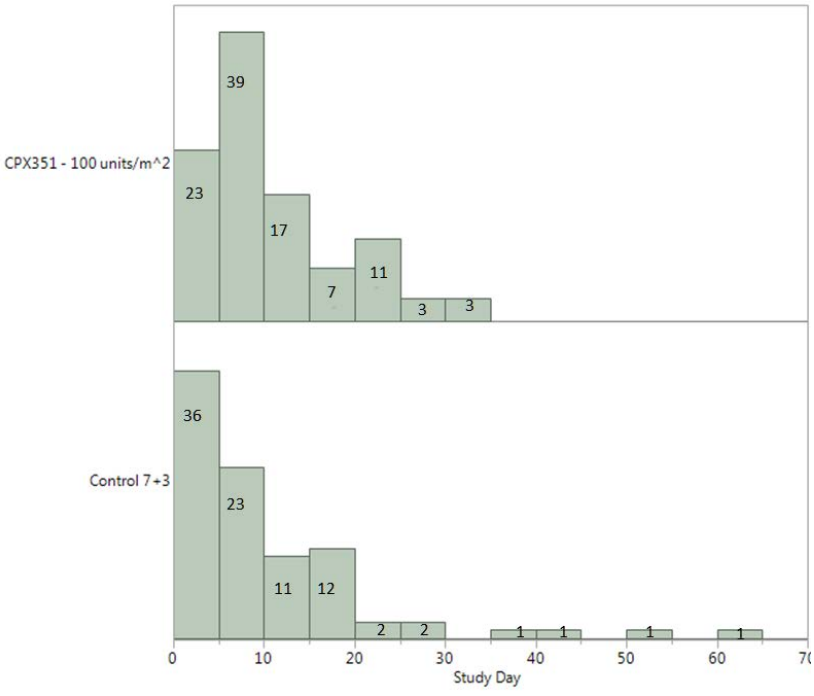
(b) (4)

(b) (4)

Neurologic/Psychiatric AEs and Copper Levels

As detailed above, more patient on the CPX-351 arm (128/153, 84%) experienced TEAEs in the Nervous system disorders and Psychiatric disorders SOCs as compared to patients on the control arm (111/151, 74%). Neuropsychiatric events are well-described manifestations of copper toxicity, most strikingly in but not limited to patients with WD. Since in the applicant's analysis of copper levels (detailed in Figure 25 above), the elevated levels in the CPX-351 arm had for the most part returned to near baseline in most patients by day 14 of induction 1, FDA performed an analysis of time to first neuropsychiatric event in patient during induction 1 of the trial. 197 patients experienced their first neuropsychiatric event on the trial during induction 1; 106 (69%) in the CPX-351 arm and 91 (60%) in the control arm. Excluding hemorrhagic events and brain masses, as these do not reflect copper toxicity, there were 103 patients on the CPX-351 arm (67%) and 90 patients on the control arm (60%) who experienced a neuropsychiatric event during induction 1. The median time to onset of these events were day 8 in the CPX-351 arm (range: 1-31) and day 6 (range: 1-60) in the control arm; notably, 81 patients on the CPX-351 arm (53%) experienced onset on or before day 15 and only 24 (16%) had onset after day 15. In those with onset after day 15, 5% had onset between days 15 and 20 and 7% had onset between days 20 and 25.

Figure 30: Study 301- TEAEs in the Nervous System or Psychiatric Disorders SOCs During Induction 1, by Study Day



Source: FDA reviewer
Numbers in boxes are number of patients with first event on that study day or time period.

The most common TEAEs in these SOCs on the CPX-351 arm during induction 1 were headache (20%), sleep disorders (11%), anxiety (9%), dizziness (8%), delirium (4%), altered state of consciousness (3%), depression, peripheral neuropathy, presyncope (2% each), dysgeusia and hallucinations (1% each) and agitation, amnesia, disorientation, psychomotor hyperactivity, restlessness, syncope and tremor, which occurred in 1 patient each. Median duration of these toxicities was 5 days (range 1-202 days). The events with onset on or before induction 1 day 15 included headache (14%), sleep disorders (10%), dizziness and anxiety (7% each), delirium (3%), depression, dysgeusia, hallucination, altered state of consciousness and peripheral neuropathy (1% each) and agitation, amnesia, disorientation, restlessness, syncope and tremor (1 patient each).

In the control arm, sleep disorders (14%) and headaches (13%) were the most common TEAEs in these SOCs during induction 1 as well, although both occurred at a lower rate than on the CPX-351 arm. Dizziness (6%), anxiety and delirium (5% each), altered state of consciousness, dysgeusia and peripheral neuropathy (3%) followed, hallucinations, sleep disorders and tremors each occurred in 1% of patients, and agitation, depression, memory impairment, peroneal nerve palsy, psychomotor hyperactivity and sinus headache occurred in 1 patient each. Median duration of these toxicities was 7 days (range 1-126 days). Seventy patients (48%) experienced TEAEs in these SOCs by day 15 in this arm. All but 1 of the sleep disorders (13%) and most of the headaches (11%) occurred during this period; the other events with onset on or before day 15 included anxiety, dizziness and delirium (5% each), dysgeusia (3%), altered state of consciousness, sleep disorder and tremor (1% each) and agitation, depression, peripheral neuropathy and psychomotor neuropathy (1 patient each).

These toxicities were mostly grade 1-2 in both arms (52% in the CPX-351 arm and 45% in the control arm), and no grade $\geq$ 4 events occurred during this period. Median AE duration for those toxicities that began on or before day 15 was 7 days in each arm, with a range of 1-202 days in the CPX-351 arm and 1-126 days in the control arm. Notably, only 11 patients (7%) in the control arm had an AE duration that was 40 days or longer, compared to 17 patients (11%) on the CPX-351 arm, and while only 2 patients had an AE duration of 100 days or longer on the control arm, 7 patients (5%) on the CPX-351 arm had these AEs last for over 100 days.

To characterize the neuropsychiatric toxicities in each arm with continued treatment, FDA analyzed TEAES in these SOCs by cycle in each arm. The results are summarized in Table 52 below:

Table 52: Neuropsychiatric Adverse Reactions, Study 301

Cycle	CPX-351	7+3
Induction 2		
Subject incidence	29/48 (60%)	26/51 (51%)
Median time to onset, days (range)	7 (1-42)	8 (1-32)
Median duration, days (range)	7 (2-131)	2.5 (2-119)
Consolidation 1		
Subject incidence	10/49 (20%)	13/32 (40%)
Median time to onset, days (range)	6 (1-27)	11 (1-41)
Median duration, days (range)	4.5 (1-72)	16 (2-49)
Consolidation 2		
Subject incidence	13/23 (56%)	4/12 (33%)
Median time to onset, days (range)	12 (1-33)	4 (1-15)
Median duration, days (range)	10 (2-80)	5 (3-34)

Note: percentages are of the total number of patients in each arm who received that cycle. Days are from the first dose of that cycle, with day 1 = first dose of the cycle.
Source: FDA reviewer

In summary, the manifestations of neuropsychiatric toxicity and their time distribution are not highly dissimilar between the treatment arms, but the incidence of these events is higher in patients treated with CPX-351 than those treated with 7+3, including through day 15 of induction 1 (53% vs 48%), when copper levels are still elevated in the CPX-351 arm. When looking at each treatment cycle, with the exception of consolidation 1, the incidence remains higher in the CPX-351 arm. With induction 2 and consolidation 2, the difference between the incidences in each arm increases: 9% difference during induction 2 and 23% difference during consolidation 2. Also, the difference in the range of onset of these toxicities appears prolonged in the CPX-351 arm when compared with the 7+3 arm, again with the exception of consolidation 1.

Reviewer comment: The increase in neuropsychiatric toxicities in the CPX-351 arm is consistent in all cycles with the exception of consolidation 1, and this inconsistency does not appear to have a plausible underlying rationale. The totality of the data point to an increase in these toxicities and in the range of their time to onset, as well as duration of toxicity, in the CPX-351 arm. The majority of the first event in these SOCs occurs concomitantly with the increase in serum copper levels during the first 15 days of induction 1, although this is true for the control arm as well, without accompanying copper levels. It is possible that the increased copper levels in these patients exacerbates the neuropsychiatric toxicities already seen with 7+3 therapy, which would account for the increase in toxicities of this nature in the CPX-351 arm. However, since Study 301 only called for collection of serum copper levels during induction 1, 30-45 days after induction, and no earlier than 30-45 days after the last treatment, a robust analysis of the correlation or lack thereof between these toxicities and serum copper levels is not possible. The low grade nature of the toxicities and their resolution

does not warrant a warning and precaution regarding in labeling. Better characterization of serum copper levels over time might be especially helpful in determining the risk: benefit for patients with WD and t-AML or AML-MRC, but the expected extreme rarity of this occurrence does not warrant a PMR.

As noted above, patients treated with CPX-351 did not have notable elevations of their bilirubin or transaminases; however, median transaminases do increase slightly baseline on day 7 of induction 1, and this remains higher than the change seen in the control arm through day 21 for both AST and ALT, which might further support the notion that acute elevation in serum copper levels might be having a transient effect in these patients. Again, the fact that hepatic function changes do not rise to the level of toxicity during this period is such that these changes do not add to the information accrued from the analyses described above.

The review team consulted with the Division of Gastroenterology and Inborn Errors Products (DGIEP) (b) (4) ***. They agreed that withholding CPX-351 treatment due to a potential concern for fulminant hepatic failure attributable to acute copper overload in patients with Wilson's disease may deprive these patients to access to a treatment with a demonstrated survival benefit, given mitigation strategies, such as albumin hemodialysis, that can help with removal of excess copper. They agree that a warning and precaution is necessary, however. Given that neither albumin hemodialysis or molecular adsorbents recirculating system (MARS), the 2 effective mitigation strategies for these patients, are not FDA approved, they recommended language in labeling that explicitly recommends that treating oncologists should consult with a hepatologist and a nephrologist with expertise in managing the potential of acute copper toxicity in patients with Wilson's disease.***

Infusion Related Reactions

As a liposomal product, the risk of infusion related reactions with CPX-351 treatment must be evaluated. The infusion related reactions described in the PI for DaunoXome consists of a triad of back pain, flushing, and chest tightness, which typically occurs at the beginning of the infusion. Non-liposomal daunorubicin has been associated with rare anaphylactoid reactions, as well as fever and chills. Cytarabine has been associated with sudden respiratory distress, rapidly progressing pulmonary edema and cardiomegaly which can be fatal. However, as described above, vital sign monitoring across the development program was inadequate to detect infusion related reactions. Some of the safety findings, for example, the much higher risk of grade $\geq$3 hypotension in the CPX-351 arm compared to the control arm (6% vs <1%, although the overall rate of hypotension was the same in both arms (22%)) raise the concern that these infusion related reactions might have been missed in the clinical trials, and the rate of grade $\geq$3 hypotension in the pooled safety database is similar at 5%. More information regarding characterization of these events is critical for potential risk mitigation strategies such as infusion interruption, supportive medications, and potential for rechallenge.

Due to the much higher rate of rash in the CPX-351 arm compared to the control arm on the

pivotal trial and across the development program, FDA performed an analysis to explore whether this, too could be a manifestation of infusional toxicity. This does not appear to be the case, as in both arms, the majority of patients experienced rash with the first induction cycle, but at a median onset of day 10 (range 1-55) on the CPX-351 arm and 9 (range 1-42) on the control arm, more likely reflecting a true adverse reaction, as it peaked during the time of peak cytopenia.

Reviewer comment: as stated above, a PMR is necessary to better characterize infusional toxicity with CPX-351 treatment.

Use in Pregnancy

As a 505(b)(2) application for a new combination product in which the active ingredients have been previously approved individually (see pharmacology/toxicology and clinical pharmacology sections), the applicant submitted a study report on previous human experience to support VYXEOS approval, namely PK data for non-liposomal daunorubicin and cytarabine, known toxicities associated with daunorubicin and/or cytarabine (cardiotoxicity, hypersensitivity, hepatic and renal impairment, hyperuricemia, tissue necrosis and drug-drug interactions). While they proposed language in section 8.1 of the label to advise patients to avoid becoming pregnant while taking VYXEOS, and of the potential harm to the fetus if taken during pregnancy, as well as a warning and precaution regarding embryofetal toxicity, they did not propose inclusion of any human data in this section of the label. In response to an Agency IR regarding a summary of human data for the reference listed drugs, the applicant summarized the literature, which included reports of fetal malformations in pregnant patients treated with anthracyclines and cytarabine during the first trimester. For cytarabine, there were 4 cases of limb malformations after first trimester exposure to cytarabine alone or in combination. The prescribing information for cytarabine and liposomal cytarabine (DepoCyt, approved only for intrathecal use) include cases of major limb malformations in infants whose mothers were exposed to cytarabine during the first trimester.

Reviewer comment: In the DepoCyt label, this information follows a sentence stating that "the systemic exposure of cytarabine following intrathecal administration of DepoCyt is negligible," yet the information regarding these cases is still included. With VYXEOS, which is systemically administered and with which systemic exposure to cytarabine is expected and necessary, this information should be included as well.

7.4.6. Safety Analyses by Demographic Subgroups

TEAEs by Age Group

Of the 365 patients who got CPX-351 at the proposed 100 units/m^2 induction dose across the development program, 161 were under 65 years of age and 204 were ≥ 65. Since the pivotal trial enrolled only patients 60-75 years of age, most of the population in that trial was ≥65 (75% on the CPX-351 arm and 74% on the control arm);the toxicity profile across the pooled safety

database is not significantly different in the two age categories, although the rates are slightly higher for all categories in the patients ≥65. The AE categories with the most striking differences between the age groups were hemorrhage which occurred at a rate that was 16% higher in the older patients, followed by edema, which also had a risk difference of ≥15% between the two age groups. A listing of notable TEAEs by age group across the pooled safety population is shown below in Table 53; included are only TEAEs with a risk difference of 5% or greater between the groups. Also excluded are AE categories for which relationship to the study drug is not apparent, or that are not deemed clinically relevant (i.e. petechaie, hemorrhoids).

Table 53: TEAEs by age category, Pooled Safety Population, CPX-351 100 units/m2

	Any grade		Grade ≥ 3	
PT[a]	≥65 N=204	<65 N=161	≥65 N=204	<65 N=161
Hemorrhage	151 (74%)	94 (58%)	31 (15%)	16 (10%)
Edema	125 (61%)	74 (46%)	8 (4%)	3 (2%)
Cough	83 (41%)	43 (27%)	-	-
Hypoxia	47(23%)	17 (11%)	28 (14%)	9 (6%)
Delirium	42 (21%)	15 (9%)	7 (3%)	2 (1%)
Diarrhea/colitis	112 (55%)	71 (44%)	12 (6%)	10 (6%)
Febrile neutropenia	140 (69%)	95 (59%)	137 (67%)	94 (58%)
Pulmonary edema	22 (11%)	2 (1%)	5 (2%)	-
Dyspnea	83 (41%)	52 (32%)	31 (15%)	18 (11%)
Fungal infection	48 (24%)	22 (14%)	23 (11%)	11 (7%)
Pneumonia (excluding fungal)	61 (30%)	35 (22%)	47 (23%)	27 (17%)
Dysphagia	20 (10%)	4 (2%)	2 (1%)	1 (1%)
Hallucinations	18 (9%)	4 (2%)	1 (0.4%)	-
Bacteremia (excluding sepsis)	49 (24%)	29 (18%)	45 (22%)	24 (15%)
Mucositis	111 (54%)	78 (48%)	3 (1%)	6 (4%)
Chills	67 (33%)	45 (28%)	1 (0.4%)	-
Tremor	15 (7%)	4 (2%)	-	1 (1%)
Altered state of consciousness	25 (12%)	12 (7%)	9 (4%)	2 (1%)
Abdominal pain	78 (38%)	54 (34%)	6 (3%)	5 (3%)
Pleural effusion	36 (18%)	21 (13%)	2 (1%)	2 (1%)
Dizziness	51 (25%)	33 (20%)	2 (1%)	1 (1%)

Source: FDA reviewer analysis
[a]Includes grouped terms (see Appendix 13.5)

In addition, for the category "Arrhythmia," patients in both age groups had a 30% rate of this toxicity; however, the risk of grade ≥3 arrhythmia was higher in the older age category (6% vs 2%).

Reviewer comment: These data provide sufficient evidence of safety in the population of adult patients under 60 years of age not enrolled in the pivotal study, supporting extension of

the indication to all adult patients rather than restricting it to the 60-75 year old age group enrolled in the pivotal study. The slightly increased rates of many of the toxicities in the older population are consistent with those seen across intensive therapies in this population of patients.

TEAEs by Sex

There were 211 males and 154 females treated at the proposed CPX-351 dose and schedule across the pooled safety population. The toxicity profiles were relatively similar between both sexes; the only TEAE with a risk difference of 15% or more between the arms was vomiting, which occurred in 41% of females and 23% of males. TEAEs in which the risk difference was between 10 and 15% included nausea (62 % in females and 49% in males), and hypotension and edema, both of which occurred at a lower rate in females than males (17% vs 27% and 47% vs 60%, respectively).

TEAEs by Race

Only 44 patients (12%) treated at the proposed CPX-351 dose and schedule across the pooled safety population were non-white, such that an analysis by race is limited by small numbers. The majority of non-white patients were black or African American (6%), with a minority of patients who were Asian (2%) and 3% identified as "other".

The toxicity profile for these patients mirrored that seen in Study 301 and across the pooled safety database. The rate of hemorrhagic events was slightly higher, at 82%, with 9% of these between grade ≥3. Otherwise, events that occurred in this population at a rate that was >10% higher than that of the pooled safety population included peripheral neuropathy (14%), diarrhea/colitis (61%) and vomiting (36%). Events that occurred at a lower rate in this population included rash (45%), although the rates of grade ≥3 were higher in this population at 9%, and edema (36%).

Reviewer comment: The numbers by race are limited, but overall the safety review by demographic subgroup does not indicate any safety signal that warrants a limitation of use or other labeling tool to protect people in a particular demographic subgroup.

7.4.7. Specific Safety Studies/Clinical Trials

With the exception of the dedicated QT study referred to above (section 7.4.4), no studies were conducted to evaluate a specific safety concern, or to evaluate safety in a particular patient population, as part of the CPX-351 clinical development program.

However, Study 101 was a phase 1 dose-finding study that enrolled patients ≥ 18 years of age with AML in second or greater relapse, first relapse with first CR of <6 months or who were refractory to induction therapy, and patients with primary refractory disease, as well as patients with relapsed/refractory ALL other than T-cell ALL, which was allowed only in patients

who had received prior nelarabine treatment, and patients with MDS who had RAEB-2 with >10% blasts after treatment with an HMA. The primary objective was to determine the MTD which would then be the RP2D. Thirty four patients were treated at dose levels of 3, 6, 12, 24, 32, 43, 57, 76, 101, or 134 units/m^2 CPX-351 by intravenous infusion over 90 minutes on Days 1, 3, and 5, and an extension cohort of 14 patients were treated at the RP2D. Treatment consisted of CPX-351 treatment as above during Induction 1. A second induction was given at the same dose and schedule as the first if:

- The day 14 BM evaluation indicated aplasia
- Follow-up BM biopsy showed at least a 50% reduction in blast percent to 5-25%, and there was evidence of rising peripheral blood counts or increased BM cellularity
- At least 28 days had elapsed since the start of induction 1

Patients in CR could receive 1 cycle of consolidation at the same dose and schedule, and the timing and criteria to administer this cycle were left to the discretion of the investigator.

The DLT observation period was the first cycle of therapy, and DLT criteria included:

- Hematologic: no evidence of AML, persistent BM cellularity of <20% , and peripheral ANC of <500/mcl and/or platelet count <10,000/mcl, or persistent platelet transfusion dependence.

Reviewer comment: the timing and degree of cytopenia included in this DLT definition are quite liberal and could account for the toxicity seen in subsequent studies that ultimately led to a decreased schedule in induction 2 (2 vs 3 doses), and a decreased dose and schedule in consolidation (65 units/m^2 x 2 doses rather than 100 units/m^2 x 3 doses).

- Non-hematologic toxicity grade 3-4 with fairly standard exceptions for nausea/vomiting that responded to anti-emetic therapy, grade 3 mucositis would only be considered a DLT if it lasted >7 days (although there was no stipulation that patients requiring NGT/TPN would be considered DLTs), and grade 3 febrile neutropenia.
    - Diarrhea was also excepted in that grade 4 had to occur in the presence of grade 4 neutropenia or with an unknown etiology to be considered a DLT.

The study used an accelerated titration of 1 patient per cohort unless toxicity was observed (grade 2 or greater) or until a PD effect was noted. PD effect was defined as reduction in BM cellularity by >50% with reduction in blasts. When a PD effect was seen, a second patient was to be enrolled in that cohort, and if that patient experienced a PD effect, this triggered a 3+3 design for subsequent cohorts. If the second patient did not experience a PD effect, single patient cohort dose escalation continued. If a DLT occurred at any time, up to 5 additional patients would be enrolled at the same dose and if $\geq$2 patients experienced a DLT, dose escalation stopped.

Ultimately, the following numbers of patients were enrolled in the following dose cohorts:

Figure 31: CPX-351 Dose Level Enrollment, Study 101

Dose				Patients Entered	
Level	CPX-351 units/m^2	Cytarabine mg/m^2	Daunorubicin mg/m^2	Escalation Phase	Extension Phase
1	3	3	1.32	1	
2	6	6	2.64	1	
3	12	12	5.28	2	
4	24	24	10.6	4	
5	32	32	14.08	4	
6	43	43	18.92	4	
7	57	57	25.08	3	
8	76	76	33.44	3	
9	101	101	44.44	6	14
10	134	134	58.96	6	

The first PD effect was seen at dose level 4, and the first CR was seen at dose level 6 (43 units/m2), in one patient with AML and one patient with ALL.

Exposure by Cohort, including number of cycles, number of CPX-351 doses, and cumulative CPX-351 dose are summarized in Figure 32 below. Two cycles did not complete even one induction cycle due to AEs leading to treatment discontinuation. Most patients (24, 50%) received 1 induction cycle, 13 patients (27%) received 2 inductions cycles, and 2 patients received 3 induction cycles despite the fact that this was not part of the protocol allowance. Seven patients (15%) received one cycle each of induction and consolidation.

Figure 32: CPX-351 Exposure (Cycle, Dose) by Dosing Cohort in Study 101

Patient ID	Cohort	DOSE (units/m^2)	Induction courses	Consolidation courses	Total # of CPX-351 doses	Estimated cumulative CPX-351 dose (units/m^2)	Best Leukemia Outcome	Off Study Reason
(b) (6)	1	3	1	--	3	9	--	PD
	2	6	1	--	3	18	--	PD
	3	12	1	--	3	36	--	PD
	3	12	2	--	6	72	--	PD
	4	24	1	--	3	72	--	other
	4	24	2	--	6	144	--	PD
	4	24	3*	--	10	240	--	PD
	4	24	1	--	3	72	--	PD
	5	32**	2	--	6	192	PR	PD
	5	32	2	--	6	192	PR	PD
	5	32	1	--	3	96	--	PD
	5	32	2	--	6	192	CRp	PD
	6	43	1	--	3	129	CR	Complete
	6	43	1	--	3	129	--	PD
	6	43	0	--	2	86	--	Death
	6	43	1	1	5	215	CR	PD
	7	57	1	--	3	171	F	PD
	7	57	2	--	6	342	--	PD
	7	57	3	--	9	513	--	PD
	8	76	1	--	3	228	--	PD
	8	76	1	1	5	380	CR	PD
	8	76	1	--	3	228	--	PD
	9	101	1	--	3	303	F	PD
	9	101	2	--	6	606	--	Other
	9	101	1	--	3	303	--	PD
	9	101	1	--	3	303	--	Death
	9	101	1	--	3	303	--	Other
	9	101	2	--	6	606	--	PD
	9	101	1	--	3	303	CR	Discretion
	9	101	1	--	3	303	--	PD
	9	101	1	--	3	303	--	AEs
	9	101	0	--	2	202	--	AEs
	9	101	1	--	3	303	--	Death
	9	101	2	--	6	606	F	PD
	9	101	1	1	5	505	CR	Complete
	9	101	1	1	5	505	CR	Complete
	9	101	1	1	5	505	CR	Complete
	9	101	2*	--	8	808	PR	Complete
	9	101	2	--	6	606	F	PD
	9	101	1	1	5	505	CR	Complete
	9	101	2	--	6	606	--	Lost
	9	101	1	--	3	303	--	PD
	10	134	1	--	3	402	--	Death
	10	134	1	--	3	402	--	PD
	10	134	1	--	3	402	--	PD
	10	134	1	--	3	402	CR	Discretion
	10	134	1	1	5	670	CR	Complete
	10	134	2	--	6	804	F	PD

Source: Applicant's CSR, CLTR 0305-101, Section 11.4.1, page 79.

DLTs at the dose above the MTD (134 units/m2) included:

- congestive heart failure (CHF) 25 days after initiation of therapy during a sepsis episode in a patient who had received prior cumulative anthracycline exposure of 369mg/m2, with an additional 177 mg/m^2 with CPX-351, for a cumulative anthracycline exposure of 546 mg/m2. LVEF recovered but not to >50% (47% from nadir of 29%, from baseline of 52%).
- Hypertensive crisis, including seizure and mental status changes (grade 4) on study day 21. She subsequently developed sepsis in the absence of evidence of progressive disease, and died on study day 36.
- Prolonged marrow aplasia: A patient who received an induction cycle of CPX-351 on day 28 of induction cycle 1 with 7+3 due to lack of response. Platelet and neutrophil recovery was delayed until day 105, at which time BM continued to reveal CR.

The MTD was thus determined to be 101 units/m^2, and 14 additional patients were enrolled in an expansion cohort to confirm its safety.

Deaths and SAEs from study 101 are included in the pooled safety analysis above.

AEs that occurred in at least 20% of patients in Cohort 10 (the dose level above the MTD) are depicted by cohort in Table 53 below.

Table 54: Non-laboratory TEAEs on Study 101, by Cohort

	All Grades							
PT[a]	12 units per m^2 N=2	24 units per m^2 N=4	32 units per m^2 N=4	43 units per m^2 N=4	57 units per m^2 N=3	76 units per m^2 N=3	101 units per m^2 N=20	134 units per m^2 N=6
Fatigue	0%	0%	75%	25%	33%	0%	70%	100%
Hemorrhage	0%	0%	25%	75%	67%	0%	60%	83%
Febrile neutropenia	50%	50%	25%	0%	67%	33%	55%	83%
Mucositis	100%	25%	75%	25%	33%	33%	50%	83%
Diarrhea/colitis	0%	50%	25%	25%	67%	33%	30%	83%
Abdominal pain	0%	25%	50%	25%	0%	0%	15%	83%
Rash	50%	0%	25%	25%	67%	33%	70%	67%
Pyrexia	50%	0%	25%	0%	33%	33%	55%	67%
Nausea	0%	0%	25%	25%	0%	67%	50%	67%
Fungal infection	0%	0%	0%	25%	0%	0%	30%	67%
Dyspnea	0%	50%	25%	50%	33%	33%	55%	50%
Oedema	0%	0%	25%	25%	33%	33%	50%	50%
Chills	0%	0%	0%	0%	67%	33%	35%	50%
Decreased appetite	0%	0%	0%	25%	67%	33%	30%	50%
Vomiting	0%	25%	25%	0%	0%	0%	20%	50%
Arrhythmia	50%	0%	50%	50%	33%	0%	15%	50%
Bacteraemia (excluding sepsis)	0%	25%	0%	0%	0%	33%	45%	33%
Constipation	0%	0%	50%	25%	33%	0%	40%	33%

	All Grades							
PT[a]	12 units per m^2 N=2	24 units per m^2 N=4	32 units per m^2 N=4	43 units per m^2 N=4	57 units per m^2 N=3	76 units per m^2 N=3	101 units per m^2 N=20	134 units per m^2 N=6
Headache	50%	0%	25%	25%	33%	67%	35%	33%
URTI	50%	25%	25%	0%	0%	33%	30%	33%
Sepsis (excluding fungal)	0%	0%	0%	0%	0%	33%	25%	33%
Cough	0%	50%	25%	25%	33%	33%	15%	33%
Hypoxia	0%	0%	0%	25%	0%	0%	15%	33%
Non-conduction cardiotoxicity	0%	25%	0%	0%	0%	0%	15%	33%
Sleep disorder	50%	0%	25%	0%	67%	33%	10%	33%
Pruritus	0%	0%	25%	0%	0%	0%	10%	33%
Depression	0%	0%	0%	0%	0%	0%	10%	33%

Source: FDA reviewer analysis
[a]Includes Grouped Terms (see Appendix 13.5)

Reviewer comment: Overall, the toxicities seen in the dose-finding study were consistent with those seen throughout the development program and in the pivotal study. Although limited by small numbers, there does appear to be a positive correlation between dose and toxicity, as is expected with a cytotoxic agent such as CPX-351.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

As previously noted in section 5.5.3, no carcinogenicity studies were conducted with CPX-351 per ICH S9. The Applicant references the known effects of the listed drugs DepoCyt® and DaunoXome®. An analysis of terms in the SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps" revealed 2 patients (1%) with these events on the CPX-351 arm and no patients on the control arm. These included 1 patient with renal cell carcinoma on study day 8 and basal cell carcinoma on study day 53.

In the pooled safety population, 8 patients who received CPX-351 (2%) had AEs in this category, all but 1 at the proposed dose and schedule. They included 3 benign neoplasms (adrenal , lung and fibroma), 1 meningioma, 1 malignant melanoma in situ, 1 bone neoplasm and the 2 carcinomas described above on Study 301. They occurred between study days 2 and 83.

Reviewer comment: The increased rate of neoplasms raise the likelihood of carcinogenicity with CPX-351, although the time points of their development in these patients is early and do not provide evidence of carcinogenicity of CPX-351 per se. However, carcinogenicity would be expected for this product given the evidence of carcinogenicity for both APIs. The information regarding carcinogenicity of daunorubicin and cytarabine should be included in section 13.1 of labeling, as recommended by the pharmacology/toxicology review team.

Pediatrics and Assessment of Effects on Growth

The applicant was granted Orphan Designation for CPX-351 for the treatment of patients with AML, and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). No pediatric data was submitted with the application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of CPX-351 in the AML population. CPX-351 does not have abuse potential.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

CPX-351 is not marketed in any country, and there is no postmarket experience.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application; it is recognized that once it is approved, its use will not be limited to those with adequate organ function and performance status to be enrolled on a clinical trial. Further, it may be used in patients may be used in populations other than those included in the indication statement. For both of these reasons, safety in the postmarket setting is not entirely predictable.

7.4.10. Integrated Assessment of Safety

The primary data in support of safety for the proposed indication came from Study 301, in which 153 patients with newly diagnosed t-AML, AML with antecedent hematologic disorders or AML with cytogenetic changes associated with MDS were exposed to CPX-351 and 151 patients were exposed to standard 7+3 induction therapy. Most patients received 1 cycle of CPX-351 therapy (42%), 39% received 2 cycles, 17% received 3 cycles, and only 3 patients (2%) received the maximum 4 cycles of CPX-351 therapy.

The study population was monitored for deaths, serious adverse events, common adverse events of various toxicity grades, and common laboratory tests. A thorough QT Study (306) was conducted. On study 301, there were 106 deaths (69%) on the CPX-351 arm, 14% due to adverse events, similar the rate of fatal adverse events on the control arm (15%). All-cause mortality by day 30 of therapy was 6% on the CPX-351 arm and 11% of those on the control arm, and by day 60 was 14% on the CPX-351 arm and 21% on the control arm. Fifteen patients on the CPX-351 arm (10%) died during study treatment or within 30 days of the last dose, compared to 26 (17%) on the control arm. The most common cause of death within 30 days of the last dose of therapy on both arms was infection (3% on the CPX-351 arm and 5% on the control arm). CNS hemorrhage was the next most frequent cause of death in the CPX-351 arm (3 patients within 30 days of therapy and an additional patient more than 30 days from the last

dose), compared to only 1 patient on the control arm. The most common AE leading to treatment discontinuation on the CPX-351 arm was cytopenia, either isolated thrombocytopenia or both neutropenia and thrombocytopenia.

Adverse events with CPX-351 were mostly similar to those seen with standard 7+3 therapy. Common TEAEs (≥20%) across all cycles of treatment included hemorrhages, febrile neutropenia, edema, rash, nausea, mucositis, diarrhea/colitis, constipation, musculoskeletal pain, fatigue, dyspnea, abdominal pain, headache, cough, decreased appetite, pneumonia (excluding fungal), arrhythmia, bacteremia (excluding sepsis), chills, sleep disorders, vomiting, non-conduction cardiotoxicity, dizziness, hypotension, pyrexia, hypoxia, chest pain, hypertension and URTI (except fungal). Of those, the ones which occurred at a rate of >3% compared to the control arm on Study 301 included hemorrhagic events (21% higher), headache and cough (10% higher for each), pneumonia (6%), pyrexia (5%), and musculoskeletal pain and URTI (4% higher for each). The most common (≥10%) AEs grade ≥ 3 in the CPX-351 arm were febrile neutropenia, bacteremia, pneumonia, dyspnea, sepsis, hypoxia, hemorrhagic events, hypertension and non-conduction cardiotoxicity. Of these, the ones that occurred at a rte of >3% compared to the control arm on Study 301 included pneumonia (5% higher), hemorrhagic events (4%) and hypertension (6%).

Supportive safety data from studies 101, 204, 205 and 206 were similar to those seen in the pivotal study, and an analysis of patients <65 (mostly from study 205) compared to those ≥65 years of age supported extension of the indication to adults ≥18, rather than just the 60-75 year old age group enrolled in the pivotal study. For the most part, AEs were slightly less common in patients under 65years of age, including (risk difference of ≥10%) hemorrhage (74% in patients ≥65 vs 58%), edema (61% vs 46%), cough (41% vs 27%), hypoxia (23% vs 11%), diarrhea (55% vs 44%), febrile neutropenia (69% vs 59%), pulmonary edema (11% vs 1%), and dyspnea (41% vs 32%).

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

- Study 205 was a negative study, as it failed to reach its primary endpoint, such that only Study 301 should be used to support labeling claims. The indication should be limited to newly diagnosed patients.
- Study 204 was a negative study, as CR rates were the same in both arms, such that the indication should be limited to only patients with t-AML or AML-MRC subtypes.

7.6. Conclusions and Recommendations

Since the trend towards OS in this study is consistent with that seen Study 301, although not statistically significant, and the safety data in this study are favorable, these can be used to support extension of the indication to adults of all ages with t-AML or AML-MRC. This review

team recommends regular approval of CPX-351 for the indication "for the treatment of adults with newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)."

Xin Gao, PhD
Primary Statistical Reviewer

Yuan-Li Shen PhD
Statistical Team Leader

Aviva Krauss, MD
Primary Clinical Reviewer

Donna Przepiorka, MD, PhD
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

9 Pediatrics

The Applicant was granted Orphan Designation for CPX-351 for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). No data regarding the use of CPX-351 in children was included in this NDA.

10 Labeling Recommendations

10.1. Prescribing Information

Many of the clinical changes to the PI stem from the fact that CPX-351 has activity that is very limited, in that its use is instead of standard induction therapy (7+3), its two APIs, for AML, and is unlikely to be used in any other clinical context, such that information in the boxed warning and warnings and precautions sections are specifically for practitioners treating patients with AML.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
HIGHLIGHTS	(b) (4)	1.Changed order to have daunorubicin first, for clarity of cumulative anthracycline exposure calculations 2.Removed (b) (4) 3. Added boxed warning not to interchange with either the individual APIs or their liposomal forms, as this might lead to potentially life-threatening dosing errors.
1 INDICATIONS AND USAGE		1. Added "newly diagnosed" (b) (4) 2. removed "(b) (4)" as this is unnecessary and potentially misleading (b) (4) 3. "Adults" added to indication statement per OND

		policy to provide clear language to prescribers as to the indicated population. 4. EPC corrected in accordance with guidance.
2 DOSAGE AND ADMINISTRATIONS	Removed (b) (4) Revised multiple components to clarify dose and schedule, include tests (cardiac function, liver and renal function, CBC) that need to be done before some/all cycles, remove (b) (4) added section 2.2 for dosage modifications.	
4 CONTRAINDICATIONS	(b) (4)	Removed a (b) (4)
5 WARNINGS AND PRECAUTIONS	1. (b) (4)	1. removed, as (b) (4) 2. added W&P for non-interchangeability (See HL above) 3. added W&P for hemorrhage based on Study 301 and ISS safety analyses 4. added cumulative anthracycline calculation for VYXEOS to the cardiotoxicity W&P 5. added a W&P for heavy metal overload, with special recommendations for patients with WD or other copper-related metabolic disorders 6. Inserted administration by IV route only from applicant's proposed section 2.1 to the tissue necrosis W&P
6 ADVERSE REACTIONS	1. Removed (b) (4) 2. Revised ARs based on a) grouped PTs and b) comparison of ARs during induction by arm, to account for the imbalance between patients on the CPX-351 vs 7+3 arm who got consolidation. 3. Separated laboratory findings from ARs	

	4. removed [redacted] (b) (4)	
8 USE IN SPECIAL POPULATIONS	[redacted] (b) (4)	Added human data from the cytarabine experience
10 OVERDOSAGE:		Deleted the entire section per 21 CFR 201.57(c)(3)(ii), which states that this section should not include information about an unapproved dosage (e.g. dosage greater than the maximum recommended dosage in Dosage and Administration section) not associated with an overdosage because this information may imply or suggest an unapproved dosage regimen. This entire section may be omitted because it does not provide specific overdosage data that would be useful to the healthcare provider.
14 CLINICAL STUDIES	[redacted] (b) (4)	1. Deleted [redacted] (b) (4) 2. Removed [redacted] (b) (4) 3. Removed [redacted] (b) (4) 4. Removed [redacted] (b) (4)

11 Risk Evaluation and Mitigation Strategies (REMS)

The safety profile of Vyxeos based on the data contained in this NDA is similar to those seen with standard induction and consolidation therapy for AML. Toxicities can be adequately managed in the postmarketing setting through product presentation and labeling. No additional risk mitigation strategies are assessed to be necessary beyond recommended labeling.

12 Postmarketing Requirements and Commitments

One clinical study to characterize infusion reactions will be required under FDAAA:

Characterize the nature, incidence and severity of infusion-related reactions in at least 50 patients treated with Vyxeos. The safety evaluation should include vital sign monitoring (temperature, pulse, respiratory rate, blood pressure, and oxygen saturation) at minimum immediately before initiation of the infusion, at 5 minutes, 15 minutes, 30 minutes, and at the end of the infusion, as well as for a prescribed period post-infusion. Characterize toxicities including changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness and any other relevant signs or symptoms, as well as infusion interruptions and details (rate, time after initial interruption, outcome) regarding re-challenge, if applicable. Submit a summary of the analysis and datasets. Final report due July, 2019.

One pharmacokinetic study will be required under FDAAA:

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Vyxeos to minimize toxicity in patients with moderate and severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Final report due June, 2021.

13 Appendices

13.1. References

Appelbaum, F.R., et al., *End points to establish the efficacy of new agents in the treatment of acute leukemia.* Blood, 2007. **109**(5), 1810-6.

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies 204, 205, 206 and 301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 999		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): n/a Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) n/a
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) n/a
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) n/a

13.3. Nonclinical Pharmacology/Toxicology

Not applicable.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, unencapsulated and total (encapsulated and unencapsulated) plasma concentrations of the active parent, daunorubicin and cytarabine, as well as the major metabolites of daunorubicin (daunorubicinol) and cytarabine (AraU) in plasma and urine samples were measured in the clinical pharmacology and biopharmaceutics studies. The mean AUClast metabolite:parent ratio 1.8% for was daunorubicinol:daunorubicin and 3.2% for AraU:cytarabine. Circulating metabolites have limited contribution to clinical efficacy and safety.

Based on published data for the non-liposomal drug products, cytarabine is primarily excreted in the urine. While daunorubicin is also subject to urinary excretion, biliary excretion plays a proportionally larger role. Following administration of CPX-351 at a dose of 44 mg/100 mg per m^2 on Days 1, 3, and 5 in 6 patients in Trial 206, the mean fraction of the dose recovered in the urine over one dose interval (48 hours) was 3.2% as unchanged daunorubicin, 5.8% as daunorubicinol, and 9.0% as the sum of daunorubicin plus daunorubicinol. In these same patients, the mean fraction of the cytarabine dose recovered in the urine over one dose interval was 1.1% as unchanged cytarabine, 69.6% as AraU, and 70.7% as the sum of cytarabine plus AraU.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total parent drugs daunorubicin and cytarabine, as well as major metabolites daunorubicinol and AraU in human plasma were obtained from Trials 101, 206 and 301. Unencapsulated fractions of daunorubicin and cytarabine in plasma, as well as daunorubicin, daunorubicinol, cytarabine and AraU in urine were obtained from Trial 206. Encapsulated drug concentrations were estimated by subtracting encapsulated from total concentrations. As > 99% of daunorubicin and cytarabine in the circulation remains encapsulated within the CPX-351 liposomes, it is appropriate to use total plasma concentrations of daunorubicin and cytarabine in Trials 101, 206 and 301 for PK analyses.

What bioanalytical methods are used to assess concentrations?

A total of 10 validated bioanalytical methods based on liquid chromatography with tandem mass spectrometry (LC-MS/MS) were used to measure total and unencapsulated plasma concentrations of daunorubicin, cytarabine, daunorubicinol and AraU in human plasma and urine samples (**Table 55**). The bioanalytical methods were validated in accordance with the US FDA Guidance for Industry "Bioanalytical Method Validation" (May 2001). The quantitative concentration ranges, storage conditions and developed LC-MS/MS methods are appropriate to determine the concentrations of these analytes in plasma and urine.

Table 55: Bioanalytical Methods used in Clinical Studies

Validation Study	Analyte	Matrix	Quantitative Range (ng/mL)	Performance Characteristics	Clinical Study
TNJR06020	Total cytarabine	Plasma	10.0 – 1000	Appendix Table 1	Study 101
TNJR06020a	Total cytarabine	Plasma	5.00 – 2000	Appendix Table 1	Study 206, Study 301
TNJR14096	Total cytarabine	Plasma	1000 – 100000	Appendix Table 1	Study 206, Study 301
TNJR06020a	AraU	Plasma	5.00 – 2000	Appendix Table 3	Study 206, Study 301
TNJR07262	AraU	Plasma	10.0 – 1000	Appendix Table 3	Study 101
TNJR06021	Total daunorubicin	Plasma	10.0 – 1000	Appendix Table 2	Study 101
TNJR06021a	Total daunorubicin	Plasma	5.00 – 2000	Appendix Table 2	Study 206, Study 301
TNJR14095	Total daunorubicin	Plasma	1000 – 100000	Appendix Table 2	Study 206, Study 301
TNJR06021	Daunorubicinol	Plasma	2.00 – 200	Appendix Table 4	Study 101
TNJR06021a	Daunorubicinol	Plasma	3.83 – 1530	Appendix Table 4	Study 206, Study 301
TNJR14057	Free cytarabine	Plasma	5.00 – 2000	Appendix Table 1	Study 206
TNJR14057	Free daunorubicin	Plasma	5.00 – 2000	Appendix Table 2	Study 206
TNJR14122	Cytarabine	Urine	250 – 100000	Appendix Table 1	Study 206
TNJR14122	AraU	Urine	250 – 100000	Appendix Table 3	Study 206
TNJR14121	Daunorubicin	Urine	5.00 – 2000	Appendix Table 2	Study 206
TNJR14121	Daunorubicinol	Urine	3.83 – 1530	Appendix Table 4	Study 206

Source: Biopharmaceutics and Analytical Methods report, Table 4.

13.4.2. Clinical Pharmacokinetics

The PK of total daunorubicin and cytarabine was evaluated in adult patients with advanced hematologic malignancies administered a CPX-351 dose of 44.4 mg/101 mg per m^2 on Days 1, 3, and 5 in Trial 101, and in adult patients with AML and MDS administered with a CPX-351 dose of 44 mg/100 mg per m^2 on Days 1, 3 and 5 in Trial 206. Parallel plasma concentration time profiles were observed for total daunorubicin and cytarabine (**Figure 33**). The comparison of PK parameters of daunorubicin and cytarabine in CPX-351 and non-liposomal formulations are summarized in **Table 56**. When administered as non-liposomal formulations, the PK of daunorubicin and cytarabine were markedly different in terms of the volume of distribution, clearance, and half-life. In contrast, when administered as components of CPX-351, the PK parameters for daunorubicin and cytarabine were similar, because more than 99% of the daunorubicin and cytarabine in the circulation remains trapped within the liposomes.

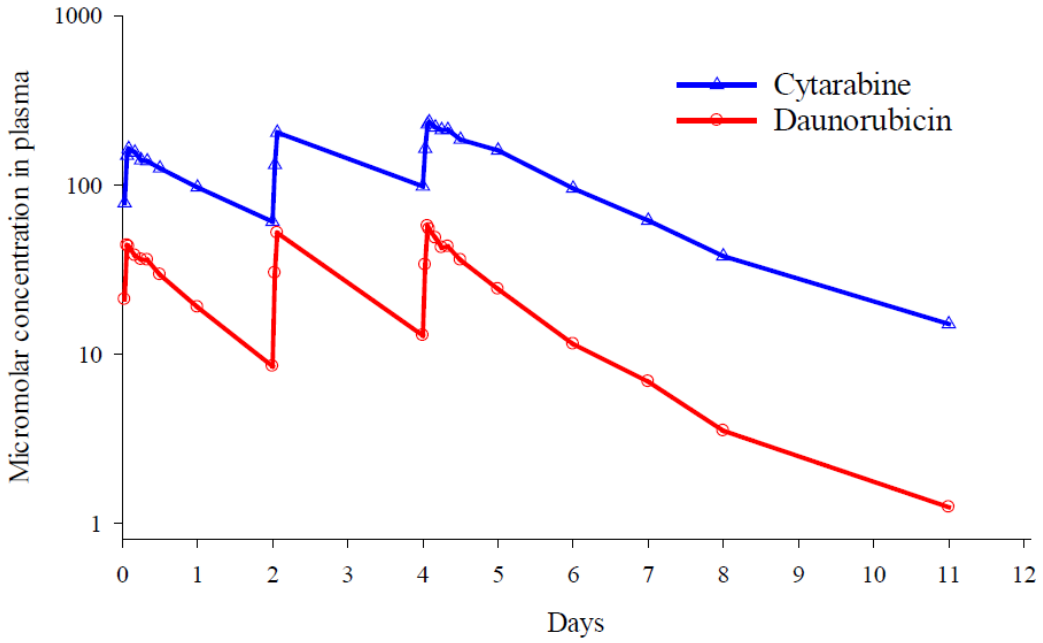


Figure 33: Mean Plasma Micromolar Concentration-Time Curves for Total Daunorubicin and Cytarabine Following CPX-351 at 44 mg/100 mg per m^2 on Days 1, 3, and 5.
Source: Trial 101 PK Report, Figure 11

Table 56: Plasma PK Parameters for Daunorubicin and Cytarabine when Administered as CPX-351 or as Non-liposomal Formulations.

PK Parameter	CPX-351		Non-liposomal	
	Cytarabine	Daunorubicin	Cytarabine	Daunorubicin
V (L)	7.11	6.64	138[a]	1364[a]
CL (L/h)	0.131	0.163	272[a]	129[a]
$t_{1/2}$ (h)	40.4	31.5	1-3[b]	18.5[c]

NOTES: Values reported are means.
V, volume of distribution; CL, clearance; $t_{1/2}$, terminal half-life
Source: Summary of Clinical Pharmacology Studies, Table 7.

The mean accumulation based on $AUC_{0\text{-}48h}$ values was 1.3 for daunorubicin and 1.4 for cytarabine based on plasma concentration-time profiles obtained on Days 1 and 5 of the induction dose schedule after administration of 44 mg/100 mg per m^2 CPX-351 on Days 1, 3, and 5 in Trial 206.

Dose proportionality was evaluated in Trial 101, where 38 patients received CPX-351 at doses ranging from 1.3 mg/3 mg per m^2 to 59 mg/134 mg per m^2 on Days 1, 3, and 5. Plots of the mean concentration-time data show that PK profiles for daunorubicin and cytarabine were essentially parallel over the dose range (**Figure 34**). Linear regression analyses of C_{max} and $AUC_{0\text{-}48h}$ versus dose indicated no significant departures from dose linearity (**Figure 35**).

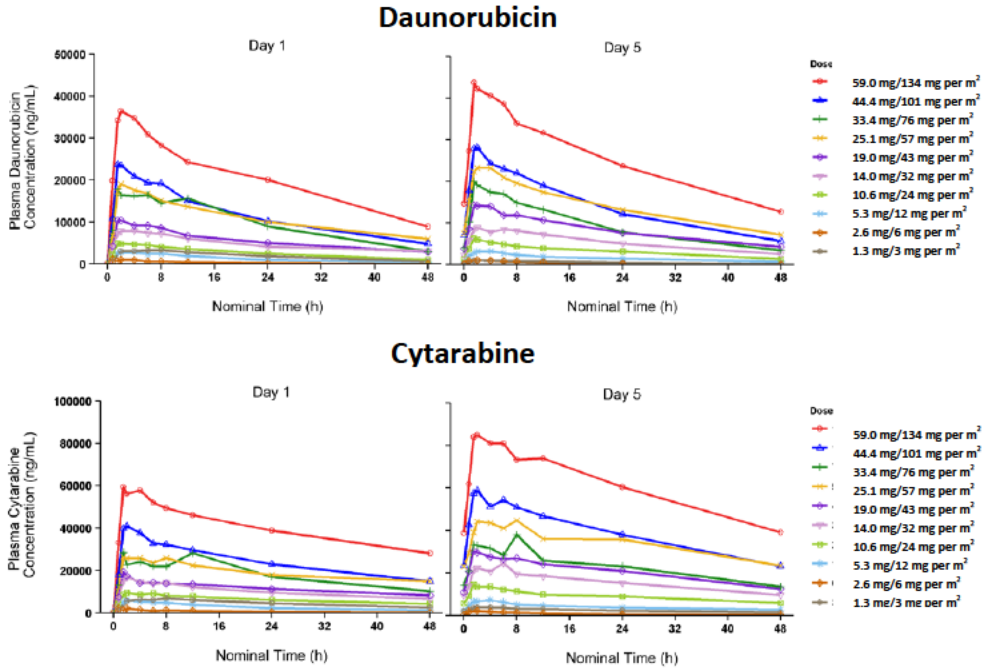
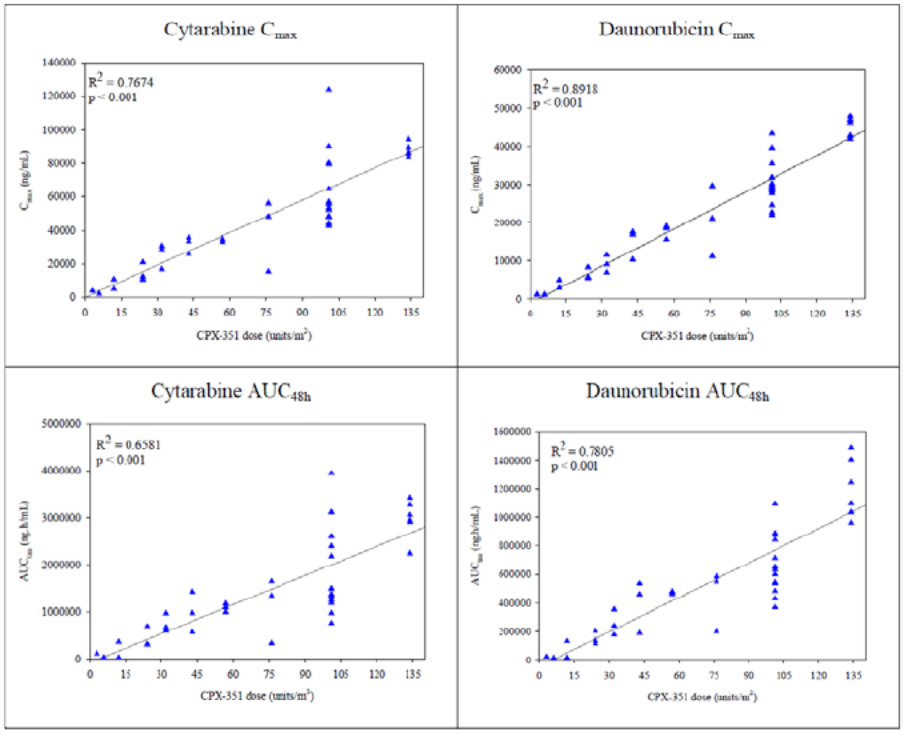


Figure 34: Mean Plasma Concentration-Time Curves for Total Daunorubicin and Cytarabine by CPX-351 Dose (1.3 mg/3 mg per m^2 to 59 mg/134 mg per m^2) for Days 1 and 5.
Source: Trial 101 PK Report, Figure 1



AUC_{48h}, area under the curve from t = 0 to 48 hours postdose; C_{max}, maximum observed concentration

Figure 35: Dose-Proportionality Assessments Based on Plasma Exposure Parameters for Total Daunorubicin and Cytarabine on Day 5.
Source: Trial 101 PK Report, Figures 16 and 17.

13.4.3. Population PK Analysis

The applicant's population PK analysis was based on pooled data (2023 daunorubicin and 2046 cytarabine PK samples available from 195 patients) from Trials 101, 206, and 301 in which patients received at least one dose of CPX-351 and had suitable records for determining dose and sample collection time for at least one plasma concentration value. Daunorubicin and cytarabine PK profiles were adequately described using a two compartmental model following IV infusion with linear clearance from the central compartment. Goodness-of-fit (GOF) plots (**Figure 36**) and visual predictive check (VPC) plots (**Figure 37**) showed there is a good agreement between observations and model predictions. The parameter estimates of final model are summarized in **Table 57**. Overall, the model-based individual predictions were consistent with the observed data.

Applicant's conclusion based on population PK analysis

- A population PK analysis of total daunorubicin and cytarabine concentration-time data administered as components of CPX-351 completed using a PK population of 195 patients with acute leukemia or MDS is suitably representative of the target population.
- Concentration-time data for daunorubicin and cytarabine were well described by a two-compartment linear PK model. The elimination half-life was 26.2 h for daunorubicin and 37.1 h for cytarabine.
- The volume of distribution of both daunorubicin and cytarabine was approximately equal to the plasma volume, suggesting that CPX-351 was essentially confined to the vasculature space.
- Daunorubicin clearance (0.14 L/h) and cytarabine clearance (0.11 L/h) were substantially lower than the non-liposomal forms of the drugs.
- The formulation (frozen versus lyophilized) did not have a clinically meaningful effect on clearance and volume of distribution. Therefore, the formulation (frozen versus lyophilized) is unlikely to correspond to detectable differences in clinical safety or efficacy.
- BSA was identified as a significant covariate, which supports BSA-based dosing. Based on covariate analyses, baseline body weight, BMI, age, sex, race and WBC count do not account for significant sources of variability in PK parameters for total daunorubicin and cytarabine.
- Based on covariate analyses and evaluations of model-based predictions of CL and AUC_{tau} in individual patients, there does not appear to be any association between plasma exposure to total daunorubicin or cytarabine and markers for hepatic function (bilirubin concentration, bilirubin category, AST, ALT, and ALP). No dose modification is recommended for patients with baseline bilirubin up to 3 mg/mL. The analysis did not include patients with bilirubin > 3 mg/dL.
- No dose modification is recommended for patients with mild renal impairment (CL_{CR} 60 - 89 mL/min) or moderate renal impairment (CL_{CR} 30 - 59 mL/min). The analysis did not include patients with severe renal impairment (CL_{CR} 15 - 29 mL/min) or end stage renal disease.

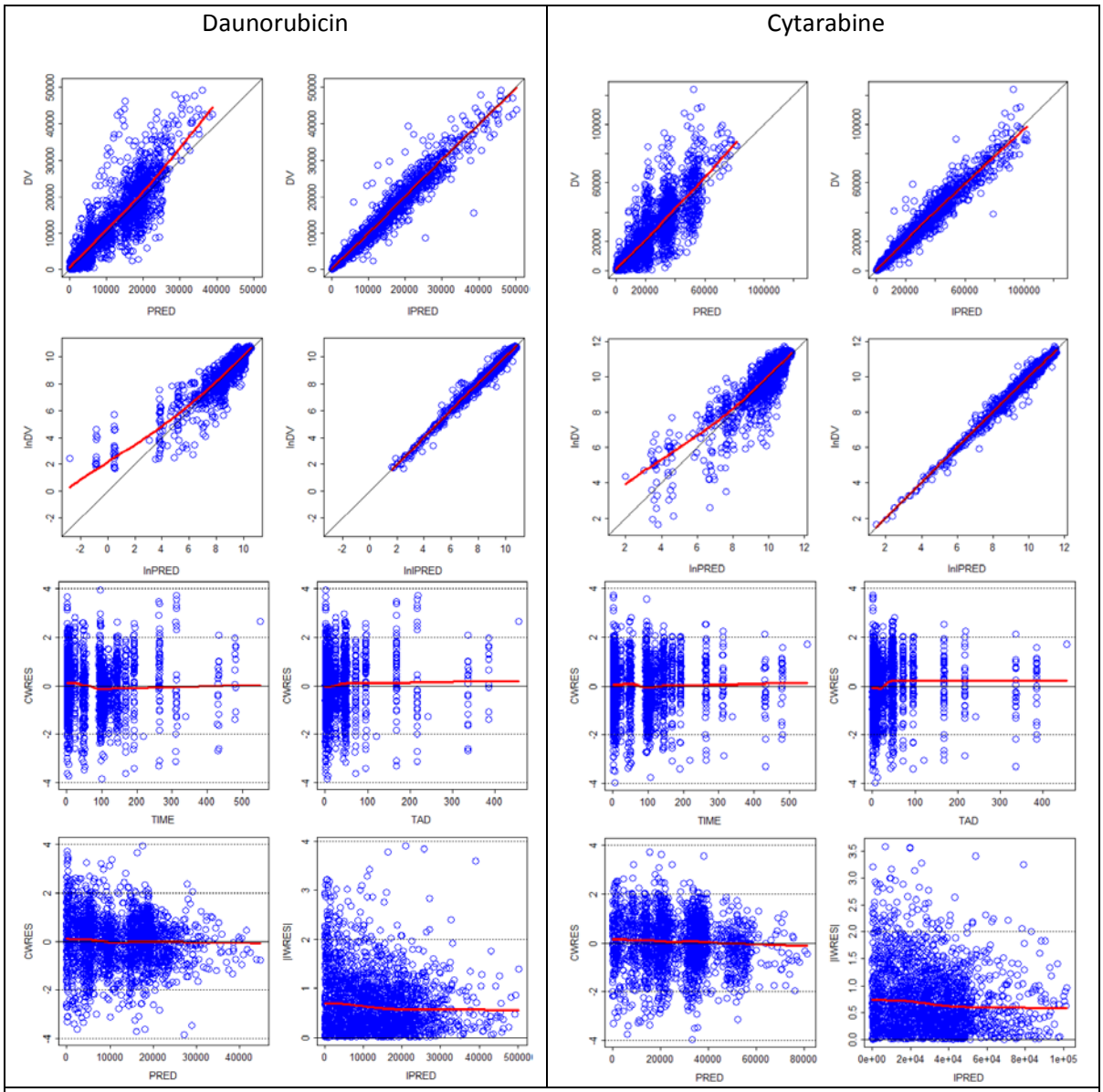
Reviewer's comments on population PK analysis

The population PK model adequately describes the observed data based on the GOF plots and VPC plots. Therefore, the model is sufficient to describe the PK of total daunorubicin and cytarabine in the dose range used to build the models and the exposure based on model predication can be used for exposure-response analyses.

Two intrinsic factors were identified as having a clinically meaningful effect on total daunorubicin and cytarabine exposure, BSA and renal function. The model includes BSA as an allometric factor on clearance and volume parameters. The baseline body weight and BMI do not appear to account for significant sources of variability in PK parameters for total daunorubicin or cytarabine after including BSA.

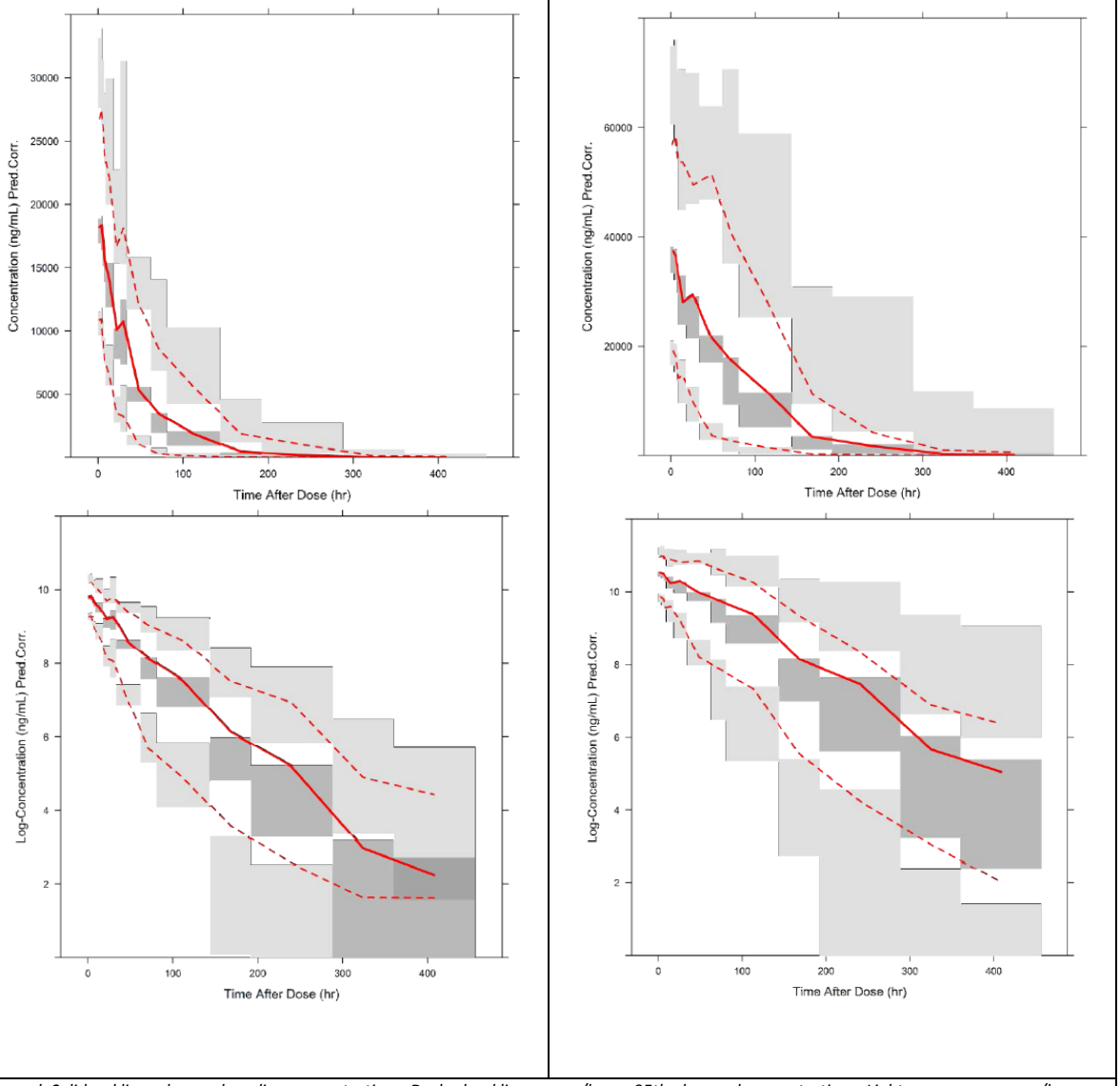
*The applicant's conclusion regarding no dose adjustment for patients with mild or moderate renal impairment is reasonable. The population PK model showed that the median exposure of total daunorubicin and cytarabine as defined by AUC_{tau} increased about 40% for patients with moderate renal impairment (**Table 58**); however, daunorubicin or cytarabine exposure for patients with moderate renal impairment at the proposed dose is about 30% to 40% lower than that from highest dose administered in Trial 101 (**Table 59**), in which dose-limiting toxicities were observed in 3 of 6 patients. In addition, E-R analysis for safety results suggested that no covariate-based dose adjustment at the commended BSA normalized dose (See Section 13.4.4). Based on the totality of the applicant's submission, the review team concludes that no dose adjustment for patients with mild or moderate renal impairment. The effect of severe renal impairment on total daunorubicin or cytarabine exposure is unknown.*

*The applicant's conclusion regarding no dose adjustment for patients with baseline bilirubin up to 3 mg/mL is reasonable. No statistically significant difference in the median total daunorubicin or cytarabine exposure (as measured by AUC_{tau}) was observed between patients with baseline bilirubin < 1.2 mg/dL and patients with baseline bilirubin from 1.2 mg/dL to 3 mg/dL (**Table 58**); however, the effect of bilirubin > 3 mg/dL on daunorubicin or cytarabine exposure is unknown.*



Legend: blue circles: observations (DV or lnDV), red line: locally weighted scatter plot smoothing (LOESS), black line: identity line.
DV: Observations; PRED: Population predictions; IPRED: Individual predictions; CWRES: Conditional weighted residuals; IWRES: Individual weighted residuals; TAD: Time after dose
Data source: Figure 7.2:2, Figure 7.2:3, Figure 7.3:2 and Figure 7.3:3 of Applicant's Population PK Analysis of Cytarabine and Daunorubicin.

Figure 36: Goodness-of-fit plots for final population pharmacokinetic models of daunorubicin and cytarabine.



Legend: Solid red line: observed median concentrations, Dashed red line: upper/lower 95th observed concentrations, Light grey areas: upper/lower 95th population predicted intervals, Dark grey areas: median population predicted interval.
Data source: Figure 7.2:4 and Figure 7.3:4 of Applicant's Population PK Analysis of Cytarabine and Daunorubicin.

Figure 37: Visual predictive check for final population pharmacokinetic model of daunorubicin and cytarabine.

Table 57: Parameter estimates of final population pharmacokinetic models

Daunorubicin

Parameter	Estimate†	BSV%
CL (L/h)	**0.145 × (BSA/1.95)$^{1.22}$** × 0.84 if Frozen Formulation	**49.4%**
Vc (L)	**4.34 × (BSA/1.95)$^{1.27}$** × 0.81 if Frozen Formulation	**24.1%**
Q (L/h)	**0.0258× (BSA/1.95)^{1}**	**80.5%, Fixed**
Vp (L)	**0.523 × (BSA/1.95)^{1}** × (Dose/86)$^{0.701}$	**80.5%, Fixed**
Error Model (Residual Variability)	15.4%	**38.9%**

Cytarabine

Parameter	Estimate†	BSV%
CL (L/h)	**0.106 × (BSA/1.95)$^{1.03}$**	70.5%
Vc (L)	**5.12 × (BSA/1.95)$^{1.16}$** × (Dose/195)$^{0.111}$	29.7%
Q (L/h)	**0.00646 × (BSA/1.95)^{1}**	80.5%, Fixed
Vp (L)	**0.214 × (BSA/1.95)^{1}**	80.5%, Fixed
Error Model (Residual Variability)	15.1%	43.3%

† Estimates are given for a typical subject with the lyophilized formulation and having BSA, and dose as shown in parentheses.
BSA: body surface area, BSV: between-subject variability, CL: systemic clearance, Q: distributional clearance, Vc: central volume of distribution, Vp: peripheral volume of distribution.
Data source: Table 7.2:2 and Table 7.3:2 of Applicant's Population PK Analysis of Daunorubicin and Cytarabine.

Table 58: Renal Impairment and bilirubin categories on AUC_{tau} based on population pharmacokinetic PK analysis

Daunorubicin

Statistics	AUCtau (ng·h/mL)				
	Renal Impairment Categories (Creatinine Clearance)			Bilirubin Categories	
	Normal (≥ 90 mL/min)	Mild (60 - 89 mL/min)	Moderate (30 - 59 mL/min)	<1.2 mg/dL	1.2 – 3 mg/dL
N	69	63	24	141	15
Arithmetic Mean	584000	655000	684000	635000	562000
SD	256000	249000	225000	255000	201000
CV%	43.8	38.1	32.9	40.1	35.9
Geometric Mean	527000	604000	647000	580000	528000
Geometric CV%	50.8	44.6	36.2	47.7	38.2
Median	531000	643000	723000	596000	531000
Minimum	123000	188000	370000	123000	240000
Maximum	1220000	1160000	1073000	1220000	975000
Lower 95% CI	524000	593000	595000	593000	460000
Upper 95% CI	644000	716000	774000	677000	663000

Cytarabine

Statistics	AUCtau (ng·h/mL)				
	Renal Impairment Categories (Creatinine Clearance)			Bilirubin Categories	
	Normal (≥ 90 mL/min)	Mild (60 - 89 mL/min)	Moderate (30 - 59 mL/min)	<1.2 mg/dL	1.2 – 3 mg/dL
N	69	63	24	141	15
Arithmetic Mean	1760000	2000000	2140000	1940000	1650000
SD	896000	986000	865000	949000	697000
CV%	50.8	48.9	40.5	48.9	42.2
Geometric Mean	1520000	1730000	1960000	1680000	1510000
Geometric CV%	65.4	66.0	46.3	65.1	46.7
Median	1630000	1820000	2280000	1820000	1390000
Minimum	202000	197000	907000	197000	543400
Maximum	4300000	5020000	3920000	5020000	3030000
Lower 95% CI	1550000	1760000	1790000	1790000	1300000
Upper 95% CI	1970000	2240000	2480000	2100000	2000000

AUC_{tau}: AUC from time 0 to 48 hours after the Day 5 dose, CI: confidence interval, CV% coefficient of variability, N: number of patients, SD: Standard deviation.
Data source: Table 7.5:1 and Table 7.3:2 of Applicant's Population PK Analysis of Daunorubicin and Cytarabine.

Table 59: Pharmacokinetics of six patients administered a dose of 59 mg/m^2 of daunorubicin and 134 mg/m^2 cytarabine of in Trial 101

Statistics	AUC_{tau} (ng·h/mL)	
	Daunorubicin	Cytarabine
N	6	6
Arithmetic Mean	1230,000	3040,000
SD	168,000	337,000
Geometric Mean	1220,000	3030,000
Median	1220,000	3090,000
Minimum	1040,000	2630,000
Maximum	1480,000	3390,000

AUC_{tau}: AUC from time 0 to 48 hours after the Day 5 dose, N: number of patients, SD: Standard deviation.
Data source: Applicant's Population PK Analysis results of Daunorubicin and Cytarabine reported data sets pkcytd5.xpt and pkdaud5.xpt

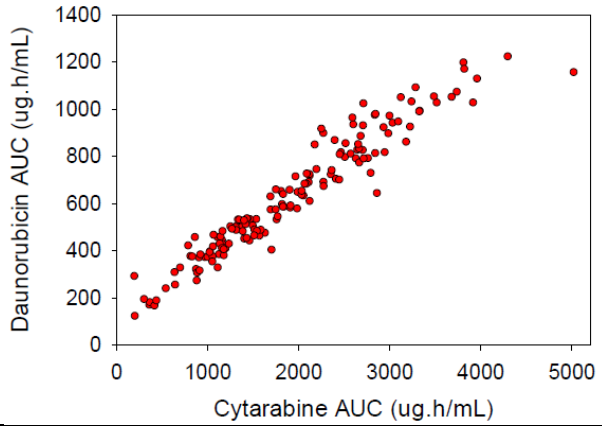
13.4.4. Exposure-Response Analyses

The exposure for total daunorubicin and cytarabine were highly correlated (**Figure 38**). Similar trends were observed for E-R analyses using total daunorubicin or cytarabine exposure. The E-R analysis discussion in this review will focus on the results from cytarabine exposure.

E-R for Efficacy

In Trial 301, the relationship between exposure (AUC_{tau}: $AUC_{0\text{-}48h}$ after day 5 dose) and primary efficacy endpoint OS was explored by Kaplan-Meier (KM) analysis for 281 patients (applicant's ER (plasma exposure) efficacy population) with PK data and were dosed on Days 1, 3, and 5 (**Figure 39**). Overall, OS benefits were better than 7+3 standard of care in all four exposure quartiles. The OS benefit from CPX-351 was greatest in the highest exposure quartile (fourth quartile in **Figure 39**). It was unclear if the OS benefit in the highest CPX-351 quartile was affected by other factors. In a multivariate analysis (**Table 60**), in addition to cytarabine exposure quartiles, factors retained in the model with $p \leq 0.05$ included karyotype and WBC count. Interactions between the exposure effect and those covariates cannot be excluded.

Reviewer's Comments: The applicant's conclusion regarding no obvious E-R relationship for efficacy is reasonable. The E-R relationship for efficacy remains inconclusive due to limited information from Trial 301—only a single dose (44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine) was studied.



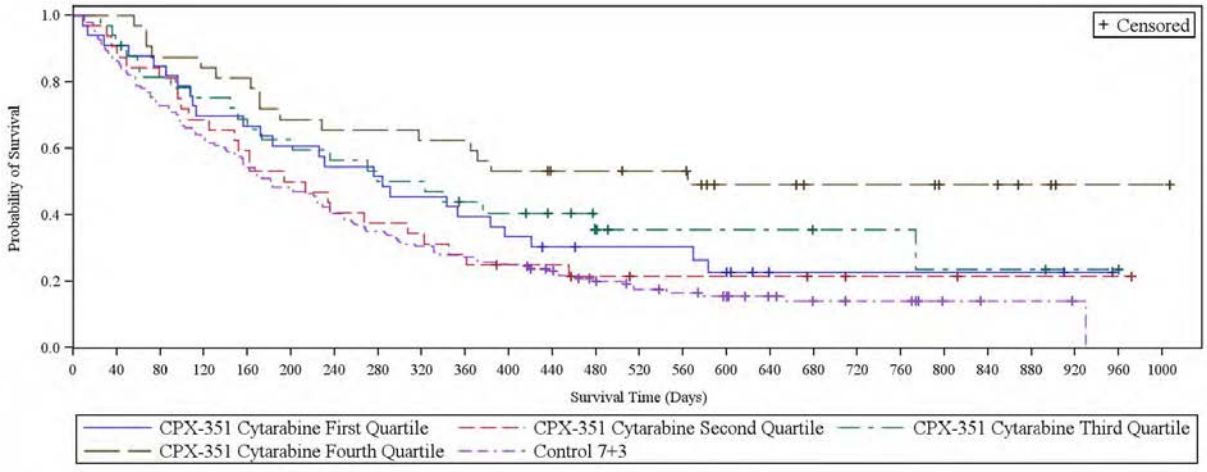
AUC: Predicted AUC_{tau}:
Data source: Figure 2 of Applicant's Exposure-Response Report.

Figure 38: Correlation between Daunorubicin and Cytarabine AUC_{tau}.

Table 60: Parameter Estimates from Multivariate Analysis of OS (Cytarabine Quartiles)

Factor	Factor Level	n/N (%)	Hazard Ratio (95% Conf. Int.)	Overall p-value
ECOG PS	0	64/262 (24.4)	0.429 (0.249, 0.738)	0.0084
	1	165/262 (63.0)	0.670 (0.428, 1.051)	
	2	33/262 (12.6)		
Karyotype	Non-poor	122/262 (46.6)	0.482 (0.340, 0.682)	<0.0001
	Poor	140/262 (53.4)		
Platelet Category	<= 50 10^9/L	162/262 (61.8)	1.460 (1.039, 2.052)	0.0291
	> 50 10^9/L	100/262 (38.2)		
Treatment Quartile	Q1	32/262 (12.2)	0.482 (0.280, 0.828)	0.0006
	Q2	28/262 (10.7)	0.710 (0.415, 1.215)	
	Q3	32/262 (12.2)	0.550 (0.325, 0.930)	
	Q4	31/262 (11.8)	0.329 (0.181, 0.600)	
	7+3	139/262 (53.1)		

Data source: Table 1.13.3 of Applicant's Response to FDA Information Request Date June 12, 2017.



		CPX-351 Cytarabine AUC (ng.hr/mL)				Control
Overall Survival	Statistic	First Quartile (N=33)	Second Quartile (N=32)	Third Quartile (N=33)	Fourth Quartile (N=32)	7+3 (N=151)
Total	n	33	32	33	32	151
Non Censored	n (%)	25 (75.8)	25 (78.1)	21 (63.6)	16 (50.0)	127 (84.1)
Censored	n (%)	8 (24.2)	7 (21.9)	12 (36.4)	16 (50.0)	24 (15.9)
Time	25%-ile (95% CI)	110.0 (28.0, 183.0)	97.5 (35.0, 152.0)	144.0 (39.0, 201.0)	171.0 (67.0, 365.0)	75.0 (53.0, 98.0)
	50%-ile (95% CI)	284.0 (156.0, 396.0)	203.5 (106.0, 322.0)	323.0 (151.0, 774.0)	564.0 (190.0, -)	181.0 (148.0, 236.0)
	75%-ile (95% CI)	583.0 (353.0, -)	408.0 (236.0, -)	774.0 (376.0, -)	-	408.0 (299.0, 515.0)
	p value (log-rank)	0.0204	0.0725	0.0087	0.0004	

Data source: Figure 1.13.1 and Table 1.13.1 of Applicant's Response to FDA Information Request Date June 12, 2017.

Figure 39: KM Analysis of OS–ER (Plasma Exposure) Efficacy Population (Cytarabine Quartiles)

E-R for Safety

The E-R for safety analyses were explored in ER (plasma exposure) safety population (n = 307) included patients in Trial 206 (n = 26) and Trial 301 (n = 281). The increase in median AUC_{tau} relative to the first quartile was approximately 1.6-, 2.3-, and 3.3-fold in the second, third, and fourth quartiles, respectively. No differences were noted among the subgroups in the incidence of TEAEs leading to treatment discontinuation or death (Table 61). The incidence of TEAE grade 3-5 increased with increasing exposure quartile. As patients who responded to treatment tended to have a longer duration of safety follow up, the higher incidence of TEAEs in the higher CPX-351 exposure groups may be at least partially confounded by favorable response to CPX-351. The applicant concluded that covariate-based dose adjustments are not indicated at the recommended BSA based dose.

Reviewer's Comments: The applicant's conclusion on the higher incidence of TEAEs in the higher CPX-351 exposure groups may be at least partially confounded by favorable response to CPX-351 is reasonable. The applicant's conclusion on no covariate-based dose adjustments is reasonable at the recommended BSA based dose.

Table 61: Overall Summary of Treatment Emergent Adverse Events–ER (Plasma Exposure) Safety Population (Cytarabine Quartiles)

Study Period Assessment, n (%)	CPX-351 First Quartile (N=39)	CPX-351 Second Quartile (N=39)	CPX-351 Third Quartile (N=39)	CPX-351 Fourth Quartile (N=39)	Control 7+3 (N=151)
Any TEAEs	39 (100)	39 (100)	39 (100)	39 (100)	151 (100)
TEAEs by Maximum NCI-CTC Grade					
Grade 1	1 (2.6)	0	0	0	2 (1.3)
Grade 2	4 (10.3)	3 (7.7)	2 (5.1)	1 (2.6)	12 (7.9)
Grade 3	18 (46.2)	23 (59.0)	24 (61.5)	26 (66.7)	92 (60.9)
Grade 4	9 (23.1)	6 (15.4)	7 (17.9)	5 (12.8)	16 (10.6)
Grade 5	7 (17.9)	7 (17.9)	6 (15.4)	7 (17.9)	29 (19.2)
Grade 3-5	34 (87.2)	36 (92.3)	37 (94.9)	38 (97.4)	137 (90.7)
TEAEs by Closest Relationship					
Not Related	3 (7.7)	0	1 (2.6)	0	8 (5.3)
Related	36 (92.3)	39 (100)	38 (97.4)	39 (100)	143 (94.7)
Serious TEAEs	21 (53.8)	20 (51.3)	22 (56.4)	23 (59.0)	65 (43.0)
TEAEs leading to disc.	1 (2.6)	0	1 (2.6)	0	2 (1.3)
TEAEs leading to death	7 (17.9)	7 (17.9)	6 (15.4)	7 (17.9)	29 (19.2)

Data source: Table 29 of Applicant's Exposure-Response Report.

13.5. Grouped Preferred Terms Used in the Safety Review

Grouped Term	Preferred Terms
Abdominal pain	abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
Abscess	anal abscess, gingival abscess, liver abscess, lung abscess, perirectal abscess, rectal abscess, subcutaneous abscess, subdriaphragmatic abscess, tooth abscess
Altered state of consciousness	altered state of consciousness, lethargy, loss of consciousness, mental status changes, somnolence
Arrhythmia	Arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block right, extrasystoles, heart rate irregular, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular tachyarrhythmia, ventricular tachycardia

Grouped Term	Preferred Terms
Bacteremia (excluding sepsis)	Bacteraemia, bacteroides bacteraemia, clostridium bacteraemia, enterobacter bacteraemia, enterococcal bacteraemia, escherichia bacteraemia, klebsiella bacteraemia, pseudomonal bacteraemia streptococcal bacteraemia
Catheter/device/injection site reacion	catheter site discharge, catheter site erosion, catheter site erythema catheter site inflammation, catheter site oedema, catheter site pain catheter site pruritus, catheter site rash, catheter site related reaction catheter site swelling, infusion site anaesthesia, infusion site pain infusion site vesicles, injection site reaction, injection site swelling
Cellulitis	Catheter site cellulitis, cellulitis, periorbital cellulitis, post-procedural cellulitis, vulval cellulitis
Chest pain	chest discomfort, chest pain, non-cardiac chest pain, painful respiration, pleuritic pain
Cholecystitis	Cholecystitis, cholecystitis acute, cholecystitis infective
Clostridial infection	Clostridium difficile colitis, clostridium difficile infection, clostridium test positive
Convulsion	Convulsion, status epilepticus
Cough	cough, productive cough
Delirium	Delirium, confusional state
Depression	Depression, depressed mood
Device related infection (except cellulitis, sepsis)	Catheter site infection, device related infection
Diarrhea/colitis	Caecitis colitis, diarrhea, enteritis, enterocolitis, enterocolitis infectious, gastroenteritis salmonella, ileitis, neutropenic colitis
Dizziness	Dizziness, dizziness exertional, dizziness postural
Dyspepsia	Dyspepsia, epigastric discomfort
Dyspnea	acute respiratory distress syndrome, acute respiratory failure, bronchospasm, dyspnea, dyspnea exertional, respiratory distress, respiratory failure, wheezing
Edema	face edema, generalized edema, edema, edema peripheral, fluid overload, fluid retention, swelling face, penile edema, scrotal edema
Eye irritation	Conjunctival oedema, conjunctivitis, dry eye, eye irritation, eye pain, eye pruritis, ocular discomfort, ocular hyperaemia, scleral hyperaemia
Eye swelling	Eye oedema, eye swelling, eyelid oedema, periorbital oedema
Fatigue	Asthenia, fatigue
Fungal infection	Aspergillosis, bronchopulmonary aspergillosis, candida sepsis, candidiasis Candiduria, fungaemia, fungal infection, fungal retinitis, fungal sepsis fungal skin infection, fungal test positive, fusarium infection, hepatic candidiasis, intertrigo candida, mycotic aneurysm, onychomycosis oral candidiasis, oral fungal infection, pneumocystis jiroveci pneumonia pulmonary mycosis, respiratory tract infection fungal, sinusitis fungal systemic mycosis, tinea cruris, tinea infection, tinea pedis, urinary tract infection fungal, vulvovaginal candidiasis, wound infection fungal, zygomycosis
Headache	headache, sinus headache

Grouped Term	Preferred Terms
Hemorrhage	anal haemorrhage, angina bullosa haemorrhagica, blood blister blood urine present, breast haematoma, catheter site bruise catheter site haematoma, catheter site haemorrhage, central nervous system haemorrhage, cerebral haemorrhage, coagulopathy conjunctival haemorrhage, contusion, ear haemorrhage, ecchymosis enterocolitis haemorrhagic, epistaxis, eye haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, haemorrhage, haemorrhage intracranial, haemorrhage subcutaneous, haemorrhage urinary tract, haemorrhoidal haemorrhage, increased tendency to bruise, injection site bruising, injection site haemorrhage intraventricular haemorrhage, lip haematoma, lip haemorrhage lower gastrointestinal haemorrhage, melaena, menorrhagia,mouth haemorrhage, mucosal haemorrhage, occult blood positive, periorbital haematoma, periorbital haemorrhage, pharyngeal haematoma, pharyngeal haemorrhage, post procedural haematoma, post procedural haematuria, post procedural haemorrhage, pulmonary alveolar haemorrhage, purpura, rectal haemorrhage, respiratory tract haemorrhage, retinal haemorrhage, scleral haemorrhage, scrotal haematoma, skin ulcer haemorrhage, stomatitis haemorrhagic subarachnoid haemorrhage, subcutaneous haematoma, subdural haematoma, subdural haemorrhage, tongue haemorrhage, traumatic haematoma, upper gastrointestinal haemorrhage, urethral haemorrhage uterine haemorrhage, vaginal haemorrhage, vitreous haemorrhage
Hallucination	Hallucination, hallucination,visual
Herpesvirus infection (except sepsis)	Herpes simplex, herpes virus infection, herpes zoster disseminated, oral herpes
Hyperbilirubinemia	Blood bilirubin increased, hyperbilirubinaemia
Hypermagnesemia	Hypermagnesemia, blood magnesium increased
Hypersensitivity	Drug eruption, drug hypersensitivity, erythema multiforme, hypersensitivity, Stevens-johnson syndrome
Hypertransaminasemia	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic function abnormal, liver function test abnormal, transaminases increased
Jaundice	Jaundice, ocular icterus
Lower respiratory tract infection	Bronchiolitis, bronchitis, bronchitis viral
Mucositis	Anal erosion, esophagitis, gastrointestinal inflammation, gingival erythema, gingival inflammation, gingival pain, gingival swelling, gingival ulceration, gingivitis glossodynia, intestinal ulcer, laryngeal oedema, lip pain, lip ulceration, mouth ulceration, mucosal erosion, mucosal inflammation, oral mucosa erosion, oral mucosal blistering, oral mucosal erythema, oral pain, oropharyngeal discomfort, oropharyngeal pain, perianal erythema, pharyngeal erythema, pharyngeal ulceration, proctalgia, proctitis, rectal ulcer, stomatitis, throat irritation, tongue blistering, tongue ulceration, vaginal inflammation

Grouped Term	Preferred Terms
Musculoskeletal pain	Arthralgia, back pain, bone pain, coccydynia, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, pain, pain in extremity pain in jaw, pelvic pain
Non-conduction cardiotoxicity	Acute endocarditis, acute myocardial infarction, angina pectoris, aortic stenosis, aortic valve incompetence, cardiac arrest, cardiac discomfort cardiac failure, cardiac failure congestive, cardiac murmur, cardiac valve disease, cardiogenic shock, cardiomegaly, cardiomyopathy, diastolic dysfunction, dilatation atrial, dilatation ventricular, ejection fraction decreased, left atrial dilatation, left ventricular dysfunction, mitral valve incompetence, myocardial infarction, pericardial effusion, pericarditis restrictive cardiomyopathy, right ventricular hypertrophy, sudden cardiac death, ventricular hypokinesia
Peripheral neuropathy	Hyperaesthesia, hypoaesthesia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, sciatica
Phlebitis	Phlebitis, thrombophlebitis, thrombophlebitis superficial
Pneumonia (excluding fungal)	Lung consolidation, lung infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia respiratory syncytial viral, pneumonia viral
Pulmonary edema	acute pulmonary edema, , pulmonary edema
Pruritis	Anal pruritis, ear pruritis, pruritis, pruritis allergic, pruritis generalized, pruritis genital
Pyrexia	Pyrexia, body temperature increased
Rash	Dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, erythema nodosum, exfoliative rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, skin exfoliation
Renal insufficiency	Acute prerenal failure, anuria, azotemia, blood creatinine increased, renal disorder, hypercreatininemia, oliguria, renal failure, renal failure acute, renal failure chronic
Sepsis (excluding fungal)	Bacterial sepsis, clostridium difficile sepsis, corynebacterium sepsis, device related sepsis, enterobacter sepsis, enterococcal sepsis, escherichia sepsis, klebsiella sepsis, neutropenic sepsis, sepsis septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal sepsis, urosepsis, viral sepsis
Sleep disorder	Insomnia, nightmare, sleep apnoea syndrome, sleep disorder, somnambulism
Thrombosis	Deep vein thrombosis, infusion site thrombosis, jugular vein thrombosis, pulmonary embolism, retinal vein thrombosis, septic embolus, subclavian vein thrombosis, thrombosis, thrombosis in device, venous thrombosis, venous thrombosis in limb
Transfusion reaction	Allergic transfusion reaction, febrile nonhemolytic transfusion reaction, transfusion reaction, transfusion-related acute lung injury
Upper respiratory tract infection (excluding fungal)	Acute sinusitis, Chronic sinusitis, nasal congestion, nasopharyngitis, paranasal sinus hypersecretion, pharyngitis, rhinitis, rhinitis allergic, rhinorrhea, sinus congestion, sinusitis, upper respiratory tract congestion, upper respiratory tract infection

Grouped Term	Preferred Terms
Urinary tract infection (excluding fungal)	Bacteriuria, Cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, urinary tract infection pseudomonal, urinary tract infection staphylococcal
Visual impairment (excluding bleeding)	Blindness, blindness transient, colour blindness acquired, diplopia, macular oedema, optic neuritis, photophobia, photopsia, photosensitivity reaction, retinal disorder, retinal ischaemia, retinal tear, uveitis, vitreous floaters vision blurred, visual acuity reduced, visual impairment
Vomiting	Retching, Vomiting

Table 62: Cardiotoxicity for Section 7.4.5

Grouped Term	Preferred Terms
Broad Cardiotoxicity	Acute myocardial infarction, Angina pectoris Aortic valve incompetence, Arrhythmia supraventricular, Arteriosclerosis coronary artery, Atrial fibrillation, Atrial flutter Atrial tachycardia, Atrioventricular block first degree, Atrioventricular block second degree Bradycardia, Brain natriuretic peptide increased, Bundle branch block right Cardiac arrest, Cardiac discomfort Cardiac failure, Cardiac failure congestive Cardiac murmur, Cardiac output decreased Cardiac valve disease, Cardiogenic shock Cardiomegaly, Cardiomyopathy, Cardio-respiratory arrest, Diastolic dysfunction Dilatation atrial, Dilatation ventricular Ejection fraction decreased, Electrocardiogram QT prolonged, Electrocardiogram ST segment abnormal, Electrocardiogram ST-T segment abnormal, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversion Extrasystoles, Heart rate increased, Heart rate irregular, Left atrial dilatation, Left ventricular dysfunction, Mitral valve incompetence, Myocardial infarction, Nodal arrhythmia Palpitations, Pericardial effusion, Pericarditis Restrictive cardiomyopathy, Right ventricular hypertrophy, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Supraventricular tachycardia, Tachycardia Tricuspid valve incompetence, Troponin increased, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular hypokinesia, Ventricular tachyarrhythmia, Ventricular tachycardiaular tachycardia, Tachycardia Ventricular arrhythmia, Ventricular extrasystoles, Ventricular tachyarrhythmia Ventricular tachycardial
Cardiac failure	Cardiac failure, Cardiac failure congestive, Cardiogenic shock, Diastolic dysfunction, Left ventricular dysfunction

14 Division Director (DHOT)

Not Applicable

15 Division Director (OCP)

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This 505(b)(2) application for a liposome for injection formulation of daunorubicin and cytarabine (Vyxeos) provides evidence for more effective use of these drugs in the treatment of adults with (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), than in the standard regimen of daunorubicin and cytarabine. In a multicenter, randomized trial of 309 patients, those treated with Vyxeos had a significantly longer overall survival than patients treated with the standard regimen. There were no significant differences in the adverse event profiles of the two treatment regimens. The overall benefit:risk evaluation of Vyxeos is positive. All review teams and consultants recommend approval of the application. The Agency and the Applicant are agreed on the product label. The application will receive regular approval.

Edvardas Kaminskas, MD
Division Deputy Director (DHP)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS
Medical Officer Review of the Consult

NDA:	209401
Sponsor:	Celator Pharmaceuticals (a Jazz Pharmaceuticals company)
Drug:	Vyxeos (CPX-351) is Cytarabine+Daunorubicin Liposomal preparation
Route of administration	Intravenous
Indication	Treatment of adults with therapy related Acute Myeloid Leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Safety Issue for Consult	Drug induced copper overload in patients with Wilson's disease
Date Received	June 29, 2017
Date review Completed	July 7, 2017
Clinical Reviewer	Ruby Mehta, MD
Team Leader	Kathleen Donohue, MD
Deputy Division Director	Dragos Roman, MD
Project Manager	Cheronda Cherry-France, RN BSN MHA

This is a DGIEP response to the request for consultation from the Division of Hematology and Oncology Products (OHOP) for NDA 209401 for Vyxeos (CPX-351), which is a Cytarabine + Daunorubicin Liposomal preparation. The consultation request regards the use of Vyxeos in patients with Wilson's disease (WD). Vyxeos contains copper (copper gluconate), and a patient receiving Vyxeos would theoretically receive up to a maximum of (b) (4) mg of copper with (b) (4) total induction doses [100 units/m^2] and (b) (4) total consolidation doses [65units/m^2]. Vyxeos treatment has been shown to confer a survival benefit of 4.5 months relative to existing therapeutic alternatives. The OHOP division has asked DGIEP whether the benefit of Vyxeos outweighs the risk of copper administration in patients with WD, given that there are no alternative treatments to Vyxeos.

Executive Summary

Patients with WD have impaired biliary excretion of copper, thereby retaining excess copper in the body. Excess copper is toxic and causes organ damage and dysfunction. There are many unknown risks when WD patients are treated with copper containing therapy, since they do not metabolize and excrete copper as a person with normal ATP7B function. About 25% of all acute myelogenous leukemia (AML) patients develop treatment related AML (t-AML) or AML with myelodysplasia-related changes (MRC). The incidence of WD is 1:30,000. A WD patient experiencing t-AML or AML-MRC would be an extremely rare event. Vyxeos treatment may lead to an acute copper overload in a patient with WD leading to fulminant hepatic failure and death. FDA unapproved therapies are available that can help in removing excess copper in the setting of acute copper overload. Therefore, withholding Vyxeos due to a potential concern for fulminant liver failure may deprive WD patients access to a treatment with a demonstrated survival benefit. The mitigation strategies include treatment with albumin hemodialysis that can help with removal of excess copper. Therefore, we agree with OHOP's recommendation to list this concern as a Warning & Precaution. We do recognize, however, that there are important limitations to this recommendation, due to the paucity of available empirical data to support it.

Though we cannot explicitly recommend non-FDA approved therapies in the label like albumin dialysis or with molecular adsorbents recirculating system (MARS), it is our opinion that these would be essential concomitant therapies to reduce the risk of acute copper toxicity in patients with WD. Thus, we intend to guide clinicians to consider this option by explicitly recommending in the label that treating oncologists consult with a hepatologist and a nephrologist with expertise in managing the potential of acute copper toxicity in patients with WD.

Wilson's disease

Wilson's disease (WD) is an autosomal recessive disease. The incidence of WD is 1:30,000, and for a WD patient to experience t-AML or AML-MRC will be an even rarer event. The genetic defect in WD is a mutation in the

ATB7B gene, which blocks incorporation of copper in ceruloplasmin, resulting in impaired biliary excretion of copper. This leads to high Cu content in the body, with accumulation in the liver. Eventually, the copper starts depositing in the other body organs, such as liver, brain (causing neurological symptoms), eyes, kidney, muscles etc. Excessive copper is pro-inflammatory and pro-oxidant and leads to organ damage and dysfunction. WD is a heterogeneous group of disorders with significant variability in serum copper/ceruloplasmin levels and clinical manifestations.

Treatment

The current FDA approved treatments for WD include chelators (penicillamine and syprine) and zinc acetate (suppresses cu absorption). The treatment of WD is life-long. Copper load is assessed indirectly via urine 24 hour copper excretion, serum non-ceruloplasmin bound copper (NCC), and total serum copper. WD patients are followed with clinical exams to assess neurological status and laboratory tests for liver biochemistry, renal function, and complete blood counts to measure the impact of Cu excess on different organ systems. Of note, chelators may cause agranulocytosis and anemia even when given at approved doses; bone marrow depression is exaggerated at higher doses. Additionally, chelators and zinc are not efficient in removing excess copper in acute settings and decoppering with these drugs takes 3 months to one year. There are unapproved therapies such as albumin dialysis and molecular adsorbents recirculating system (MARS), both of which can serve as an effective treatment in the event of acute copper toxicity.

Non-Clinical Data Submitted to NDA 209401

The sponsor submission states in the rat and dog repeat-dose toxicity studies Vyxeos caused a dose-related increase in blood copper concentration. Copper levels trended towards baseline by 7-14 days after the last dose. In rats, 12 days after Vyxeos treatment 85% of copper was excreted in the urine or feces. The sponsor states that copper-related toxicity was not observed in animals; however, full toxicity assessments were limited by the poor clinical condition of most animals. These poor and deteriorating conditions led to unscheduled euthanasia or mortality at mid-dose (10:4.4 mg/kg of cytarabine:daunorubicin) and high doses (15:6.6 mg/kg of cytarabine:daunorubicin). Both in dogs and rats, at low doses (5:2.2 mg/kg cytarabine:daunorubicin) significant GI findings and hematological toxicities were observed, but no mortality was noted. The sponsor further states the inclusion of copper gluconate in the Vyxeos formulation is acceptable given the lack of copper toxicity observed in the nonclinical studies, the limited number of lifetime doses of Vyxeos, and the potential clinical benefit to patients with life-threatening hematologic malignancies.

It is possible that copper toxicity assessment may have been obscured by other Vyxeos related toxicities that lead to poor clinical condition and premature mortality in the animal studies. In rats and dogs the copper levels peaked around Day 3 and were 8 times (rats) and 6 times (dogs) higher than baseline copper level. The mass balance studies indicate that the majority of the copper was deposited in the liver, spleen, kidney, and muscles. The serum copper levels returned to baseline within several days or a few weeks after the last dose. In animals treated with low dose Vyxeos (5:2.2 mg/kg cytarabine:daunorubicin), there were GI findings and hematological toxicities observed that could be secondary either to copper overload or to cytarabine:daunorubicin.

These non-clinical trials were performed in animal models that did not have a copper metabolism defect similar to WD patients. Certain species of dog (for example, Bedlington terriers) and sheep have mutations that cause a disease similar to WD, leading to defective copper incorporation in ceruloplasmin resulting in high serum copper load and resultant liver cirrhosis. The safety signals observed in animals that metabolize copper normally may not predict safety in WD patients.

Daily Copper Intake in Humans

The recommended daily intake of copper in healthy individuals is ~1mg/day/orally[1] and the upper tolerable limit of intake[2] is 10 mg/day. In WD patients it is recommended to avoid copper ingestion during the first year of treatment, after which limiting copper intake has been advised but no clear threshold has been proposed. The daily exposure of parenterally administered copper is ~0.3-0.5 mg/day [3] as per A.S.P.E.N.* guidelines. The Cupric Chloride injection label states that an overdose of parenteral copper can result in hemolysis, liver toxicity, including hepatic necrosis, prostration, behavior change, diarrhea, hypotonia, photophobia, and peripheral edema. A copper dose that could be safely given parenterally to WD patients could not be found in any guidelines or position papers.

Copper kinetics in humans

The average total body burden[4] of copper ranges from 50-120 mg[5] in adult males. Approximately 15-97% (on average 60%) of the copper is absorbed from dietary intake from the gastrointestinal tract. The highest concentrations of copper are in liver, heart, brain, kidneys and muscle. In healthy states, copper is bound to a mix of ceruloplasmin [93-95%] and albumin [5-7%]. In cases of acute toxicity, excess copper is predominantly bound to albumin. Biliary excretion is the major route of copper elimination and urinary excretion accounts for ~3% of copper elimination in healthy patients. The copper content of a normal adult liver ranges from 18-45 mg[5] copper per gram dry liver weight. Liver copper content > 50 mg/gram dry weight may cause liver necrosis and changes in the kidney involving necrosis of the tubular epithelium[6] and edema of the medulla.

Acute copper toxicity

Oon et al[7]. reported a case of acute copper toxicity, in which a subject injected copper glycinate 2500 mg subcutaneously. The patient developed acute renal failure requiring continuous veno-venous haemodiafiltration (CVVHDF), hemoglobinuria, acute hemolytic anemia, disseminated intravascular coagulation, acute hepatic failure with coagulopathy (INR=1.6) requiring fresh frozen plasma and cryoprecipitate, transaminitis (AST=6654 u/L and ALT=2903 U/L), dehydration, hypotension and shock requiring pressor support, and atrial fibrillation. The subject developed respiratory failure necessitating intubation, as well as injection site necrosis requiring split skin graft. Her total serum copper levels reached a maximum of 33 µmol/L (210 µg/dL) three days after the initial dose. The patient achieved a full recovery.

Toxic concentrations of copper occur [5] after the ingestion of as little as 1 g copper and the estimated lethal dose of copper in an untreated adult is about 10–20 g Cu.

Another case reported in 1977[8] described an 18 month old toddler who ingested 3 grams (3000 mg) of cupric sulfate orally [~120 mg elemental Cu/kg], and had serum copper levels of 1,650 µg/dL. The toddler experienced severe gastric irritation (vomiting, diarrhea), hemolytic anemia, oliguria, and shock. The patient was treated with peritoneal dialysis, double volume exchange transfusion, British anti-lewisite and supportive treatment. The patient fully recovered. The patient received gastric lavage and had nasogastric tube placement for removal of excess ingested cupric sulfate, so the exact ingested dose is not known with certainty. Please note that none of the patients described above had underlying Wilson's disease. Moreover, the total dose may appear large, but the actual systemic exposure likely was much lower because s/he had debridement of the injection site, while the toddler who ingested copper orally received gastric lavage. Notably, the assay may have been different, as the total serum copper

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[1] Stehle P, Stoffel-Wagner B, Kuhn KS. Parenteral trace element provision: recent clinical research and practical conclusions. Eur J Clin Nutr. 2016 Aug;70(8):886-93.
[2] Donald G. Barceloux & Dr. Donald Barceloux Journal of Toxicology: Clinical Toxicology Vol. 37 , Iss. 2,1999
[3] http://journals.sagepub.com/doi/pdf/10.1177/0884533612446706
[4] Meret S, Henkin RI. Simultaneous direct estimation by atomic absorption spectrophotometry of copper and zinc in serum, urine, and cerebrospinal fluid. Clin Chem 1971;17:360–373
[5] Donald G. Barceloux & Dr. Donald Barceloux Journal of Toxicology: Clinical Toxicology Vol. 37 , Iss. 2,1999
[6] Kurisaki E, Kuroda Y, Sato M. Copper-binding protein in acute copper poisoning. Forensic Sci Int 1988;38:3– 11
[7] Oon, S., Yap, C.-H. and Ihle, B. U. (2006), Acute copper toxicity following copper glycinate injection. Internal Medicine Journal, 36: 741–743.
[8] Walsh FM, Crosson FJ, Bayley M, McReynolds J, Pearson BJ. Acute Copper Intoxication Pathophysiology and Therapy With a Case Report. *Am J Dis Child.* 1977;131(2):149-151

reference range quoted in these publications was noted as 50 to 120µg/dL. The total serum copper reference range currently used in clinical practice is 63- 140 µg/dL[9].

Two additional pediatric cases of copper toxicity were found also in the literature, and are described briefly below.

Table 1-Pediatric cases of copper sulfate poisoning

Author	Patient Age	Copper source	Symptoms	Copper level µg/dL	Treatment	Outcomes
Walsh	1.5 years	CuSO4 solution	Emesis, coma, hemolytic anemia, hematuria	1650	Gastric lavage with milk; Dimercaprol intravenous; edetic acid and D-penicillamine	Fully recovered
Holtzman	5.5 years	Dermal exposure due to application of CuSO4 for wound debridement	hemolytic anemia, oliguria, jaundice	540	D-penicillamine	Fully recovered

Source: James LP, Stowe CD, Argao E. Gastric injury following copper sulfate ingestion. *Pediatr Emerg Care* 1999; 15: 429–31

In India, copper sulphate (CuSO4) has been used as a suicidal agent. Agarwal et al. reported that one third of cases of acute poisoning cases requiring hemodialysis were due to CuSO4 poisoning. In a case series of 66 patients presenting due to a variety of reasons for acute poisoning, 19 patients presented with acute copper toxicity of which 7 patients died. Common features in this group were: acute renal failure (ARF) (19), hematuria (3), gastrointestinal bleeding (7), intravascular hemolysis (9), jaundice (11), hepatocellular toxicity (8), methemoglobinuria (8) and circulatory collapse (5). Other articles note that ingestion of 250 mg of CuSO4 can result in systemic toxicity and CuSo4 is fatal[10] when a one gram (1000 mg) dose is ingested. In the past, CuSO4 was used as an emetic agent and given in cases of suspected poisoning. In one publication a man died after an unknown quantity[11] of CuSO4 was ingested.

Clinical Trial with Vyxeos (NDA 209401)

The Vyxeos dosing regimen in the phase 3 clinical trial includes the following copper doses:

- Induction 1: One dose (42 mg of copper/dose) on days 1, 3, 5 (total 3 doses)
- Induction 2: One dose (42 mg of copper/dose) on days 1, 3 (first dose can be given as early as day 14 after Induction 1); (total 2 doses)
- Consolidation 1: One dose (27.3 mg of copper/dose) on days 1, 3 (first dose has to be at least 35 days after day 1 of last cycle of induction); (total 2 doses)
- Consolidation 2: One dose (27.3 mg of copper/dose) on days 1, 3 (first dose has to be at least 35 days after day 1 of last cycle of induction); (total 2 doses).

(b) (4)

The sponsor states that the copper remains encapsulated within the liposomes, therefore limiting the bioavailability and duration of exposure. The exposure of

[9] http://emedicine.medscape.com/article/2087780-overview

[10] Stein RS, Jenkins D, Korns ME. Death After Use of Cupric Sulfate as Emetic. *JAMA*. 1976;235(8):801.

[11] Schwartz E, Schmidt E. Refractory shock secondary to copper sulfate ingestion. *Ann Emerg Med* 1986; **15**: 952–4.

copper is limited to a few weeks. *However, the kinetics of copper observed during the Vyxeos clinical trial do not support the argument provided by the sponsor.*

In the active control, phase 3 (Trial # 301) clinical trial with Vyxeos during the first induction period, Vyxeos was administered on days 1, 3 and 5. The baseline level of "mean" serum copper in the patients was17µg/dL (min, max of 9, and 31 µg/dL). The copper was continuously released with maximum serum copper levels observed at Day 5 i.e., serum copper peaked after the last induction dose. On day 5 the mean serum copper levels were ~125 µg/dL (min, max were 28 and 251 µg/dL, respectively). On Day 14 the mean serum copper value was ~25µg/dL (min, max of 11 and 83 µg/dL, respectively), copper levels were decreasing but the trial population did not reach the baseline value. The sponsor did not assess copper levels from Days 6 through 13; therefore it is not known whether the copper levels decreased immediately after Day 5 or slowly over a period of 10 days (until Day 14). WD patients were not enrolled in the phase 2 or phase 3 clinical trials.

The copper kinetics presented in the Vyxeos trial (i.e., in AML patients who did not have the copper trafficking defect) and the copper kinetics will be different than those in WD patients. Since WD patients have impaired biliary copper excretion, there is a greater potential that WD patient will be exposed to a high copper dose, and the cumulative chemotherapy doses may lead to copper accumulation leading to acute copper toxicity. Even though the sponsor claims the release of copper is slow, the kinetics observed during the clinical trial indicates that the serum copper release occurs soon after intravenous infusion (within ~24 hours).

Recommendations

The co-occurrence of therapy related Acute Myeloid Leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) and Wilson's disease (WD) is expected to be exceedingly rare. However, in the event that a patient with WD develops such an AML, then we think there are two potential approaches to labeling:

1. Contraindication for treating patients with WD, if alternative therapies for treatment are available, since there is a concern the patient may develop fulminant hepatic failure secondary to acute copper toxicity.
2. A boxed warning OR a Warning & Precaution (preferred because it is a rare event) to allow the treatment to proceed under the careful guidance of the patient's oncologist, as well as a hepatologist and a nephrologist, both with expertise in managing acute copper toxicity in patients with WD (preferably at a tertiary care center). A PMR with a long term registry (to follow the outcomes) in any WD patients treated with Vyxeos could be maintained for a finite duration, for example 5 years.

There are known as well as unknown risks when copper is given to patients with WD. Reasons for considering a Vyxeos treatment contraindication in WD patient include:

- Lack of non-invasive methods to quantify total copper load in the body, i.e., if a patient has a pre-existing high copper load before the start of the trial, in such a scenario exposure to an additional burden of copper will be dangerous.
- Vyxeos is an intravenous therapy, the bioavailability of copper is 100% and there is no barrier to prevent copper absorption.
- In the case of acute copper toxicity even with normal metabolic and excretory pathways, subjects experienced acute copper toxicity and presented with lethargy, vomiting, diarrhea, hemoglobinuria, anemia, jaundice, acute hemolytic anemia, hypotension/shock and few subjects experienced a fatal outcome. Patients with WD may develop hyper-acute or fulminant hepatic failure (die in 7 to 14 days) when exposed to a high copper load. FDA cannot endorse the use of albumin dialysis or MARS, as these are not FDA approved therapies for treating acute copper toxicity.

Given the underlying heterogeneity in how efficiently patients with WD metabolize copper, it is possible that one patient with the help of supportive care may be able to tolerate Vyxeos treatment, while another could suffer fulminant hepatic failure and death. (b) (4)

However, it is possible that with the help of supportive care (albumin hemodialysis or MARS) WD patients may be able to tolerate Vyxeos treatment. Therefore, withholding Vyxeos due to a potential concern for fulminant liver failure may deprive WD patients access to a treatment with a demonstrated survival benefit. The treatment of t-AML

or AML-MRC takes precedence over underlying WD. The co-occurrence of WD and t-AML or AML-MRC may be an extremely rare event and thus a boxed warning may not be suitable. In summary, we agree with OHOP's recommendation to list this concern as a Warning & Precaution.

Please consider the following points for listing this as a concern in the Warning and Precaution section:

1. Prior to administering Vyxeos, it is recommended that the treating physician measure 2 to 3 baseline values of urinary copper, total serum copper, NCC, complete blood count, liver indices, renal function, as well as perform a comprehensive baseline clinical exam including cognitive, structured neurological and psychological evaluation.
2. The modalities that "may" efficiently remove copper during acute toxicity include albumin dialysis and molecular adsorbents recirculating system (MARS). However, both are experimental therapies and are not FDA approved; they are available at limited centers and clinical experience is also limited. The copper extraction using albumin dialysis (~35 rounds of treatment) was 196 mg of copper in 2 days[12]. While Sen et al. reported serum copper reduction from 53.7 µmol/L to 35.8 µmol/L with one[13] round of treatment. Since the liposomal drug is not dialyzable, this might be an attractive option for a patient to be on concurrent albumin dialysis/MARS thereby removing the excess copper at the same time the patient is treated with Vyxeos. Treating oncologists should consult with a hepatologist and a nephrologist with expertise in managing acute copper toxicity in patients with WD.

DGIEP comment: Though we cannot explicitly recommend non-FDA approved therapies in the label like albumin dialysis with MARS, it is our opinion that these would be essential concomitant therapies to reduce the risk of acute copper toxicity in patients with Wilson's Disease. Thus, we intend to guide clinicians to consider this option by explicitly recommending in the label that treating oncologists consult with a hepatologist and a nephrologist with expertise in managing acute copper toxicity in patients with WD.

a. During the induction phase #1, if a patient develops jaundice, liver failure, coombs negative hemolytic anemia (acute onset), or worsening of renal function (oliguria or anuria), treatment must be stopped and the patient should not be re-challenged with Vyxeos.
b. Similarly, if signs and symptoms of acute copper toxicity emerge at any time point (induction or consolidation phase), the patient should be discontinued from Vyxeos and managed with supportive care. A re-challenge must be avoided, especially in patients with decompensated cirrhosis.
c. During the chemotherapy, patients should be frequently followed with serial laboratory (total serum copper, 24 hour urine copper, liver biochemical test including coagulation profile (INR specifically), complete blood count to assess for hemolysis (induced by acute copper toxicity) and clinical (structured neuropsychological and cognitive) exams.
d. A long term plan for copper balance monitoring and compliance with chelation will be required post chemotherapy.

Additional Comment

WD is underdiagnosed and sometime patients can survive into their 6 or 7th decade without knowing they have WD. Patients may have mild to moderate neuro-psychiatry problems which may be treated as atypical Parkinson's or psychosis. We recommend that sponsor tests "all" patients who are candidates for Vyxeos treatment for Wilson's disease, and confirm the WD status prior to initiating Vyxeos treatment. The patient can be evaluated by an expert hepatologist who evaluates and manages the WD patients or be tested by a gastroenterologist evaluating the patient by an algorithm provided by the WD guidelines.

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[12] Kreymann B, Seige M, Schweigart U, Kopp KF, Classen M. Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins. J Hepatol. 1999 Dec;31(6):1080-5.

[13] Sen S, Felldin M, Steiner C, Larsson B, Gillett GT, Olausson M, Williams R, Jalan R. Albumin dialysis and Molecular Adsorbents Recirculating System (MARS) for acute Wilson's disease. Liver Transpl. 2002 Oct;8(10):962-7.

Review Division Question & Background

Vyxeos is a combination of the antineoplastic drugs cytarabine and daunorubicin encapsulated in liposomes for IV administration at 5:1 molar ratio. The proposed indication for Vyxeos is adults with therapy related Acute Myeloid Leukemia (t-AML) or AML with myelodysplasia related changes (MRC), and in the pivotal trial this showed a survival advantage compared to standard 7+3 (cytarabine and daunorubicin) therapy. Due to the copper contained in the Vyxeos formulation, [redacted]. However, it is not clear that this risk outweighs the benefit for patients with Wilson's disease who have these types of AML. Can you please describe the risk to these patients if they receive all [redacted] doses of Vyxeos, as detailed below, including potential management strategy options for patients with Wilson's disease who receive this amount of copper? Please see the pertinent details regarding the copper contained in Vyxeos below, and in the attached summary.
Vyxeos contains 14% copper; the following is from the toxicology summary (see section 8.1.1. on page 25 of attached summary):

> *The maximum exposure to copper in patients under the currently proposed dosing regimen is 42.0 mg per induction dose and 27.3 mg per consolidation dose. A patient would theoretically have [redacted] mg maximum lifetime exposure to copper [redacted] total induction doses [100 units/m2] and [redacted] total consolidation doses [65 units/m2]).*

Below is the qualification of copper as an excipient, from the pharmacology/toxicology draft review:

The CPX-351 formulation contains copper gluconate which is required for stable daunorubicin encapsulation inside the liposome. Reconstituted CPX-351 contains 5 mg/mL copper gluconate, of which 14% is elemental copper. The maximum exposure of copper per dose of CPX-351 is 42 mg, while the maximum theoretical total exposure of copper under the proposed CPX-351 dosing regimen is 319 mg. The permitted daily exposure (PDE) of parenterally administered copper is 340 µg. According to the label for Cupric Chloride Injection (NDA 018960) overdose of parenterally administered copper can result in hemolysis, liver toxicity, prostration, behavior change, diarrhea, progressive marasmus, hypotonia, photophobia, and peripheral edema.

In the rat and dog repeat-dose toxicity studies CPX-351 caused a slight dose-related increase in blood copper concentration; levels trended towards baseline by 7 days after the last dose. In rats, 12 days after CPX-351 treatment 85% of copper was excreted in the urine or feces. No copper-related toxicity was observed in animals; however, full toxicity assessments were limited by the poor clinical condition of most animals.

The inclusion of copper gluconate in the CPX-351 formulation is acceptable given the lack of copper toxicity observed in the nonclinical studies, the limited number of lifetime doses of CPX-351, and the potential clinical benefit to patients with life-threatening hematologic malignancies.

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/s/

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07/13/2017

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