NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 209401 S-018**
Application Type	SE8, Response to Written Request
Priority or Standard	Priority
Submit Date	7/30/2025
Received Date	7/30/2025
PDUFA Goal Date	1/30/2026
Office/Division	OOD/DHM1
Review Completion Date	1/27/2026
Applicant	Jazz Pharmaceuticals
Established Name	(Daunorubicin and cytarabine) liposome injection
Trade Name	Vyxeos®
Pharmacologic Class	Combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor
Formulations	Injection, lyophilized [(44 mg daunorubicin and 100 mg cytarabine) liposome]
Recommendation on Regulatory Action	Approval of revised labeling

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
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
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
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
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

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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
TEAE	treatment emergent adverse event

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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 was approved in 2017 for treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). A Written Request (PWR) was issued to investigate the potential use of Vyxeos in the treatment of AML in pediatric patients 1 to < 17 years old in three studies. The results of Study 1 and Study 2 of the PWR were submitted in Supplement 006 on October 7, 2020; the supplement was approved on March 30, 2021, for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older, and revisions were added to the text in Section 8.4 of the USPI. Supplement 018 contains the results of Study 3 of the PWR, proposed labeling changes, and a request for pediatric exclusivity.

1.2 Recommendations on Regulatory Action

The review team recommends approval of the revision to USPI Section 8.4 under 505B(g)(2) of the Food, Drug, and Cosmetic Act (FD&C Act). The review team also considers the PWR to be fulfilled.

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1.3 Basis of Recommendation

Study AAML1831 (NCT04293562) included an open-label randomized comparison of Vyxeos plus gemtuzumab ozogamicin (GO) to standard chemotherapy plus GO in pediatric patients with de novo AML without a FLT3 mutation. Eligible patients were randomized 1:1 to receive 2 cycles of induction using standard daunorubicin + cytarabine + GO (Arm A) or CPX-351 + GO (Arm B). The CPX-351 dose was 60 mg/m² daunorubicin (or 2 mg/kg daunorubicin for BSA < 0.6 m²) on Days 1, 3, and 5 of Induction 1 and 50 mg/m² daunorubicin (or 1.7 mg/kg daunorubicin for BSA < 0.6 m²) on Days 1, 3, and 5 of Induction 2; the CPX-351 dose utilized was higher than the currently recommended dose of 44 mg/m² daunorubicin on Days 1, 3, and 5 in Induction 1 and on Days 1 and 3 in Induction 2. Randomization was stratified by risk group (Low Risk 1, Low Risk 2, High Risk).

The primary objective was to compare event-free survival (EFS) between Arms A and B. A sample size of 534 participants per arm would have at least 80% power with 0.05 type I error to detect a hazard ratio (HR) of 0.76 (8% difference in 5-year EFS). A secondary objective was to compare overall survival (OS) between Arms A and B. The stated sample size would have at least 80% power with 0.05 type 1 error to detect an HR of 0.72 (8% difference in 5-year OS). Interim analyses were planned at approximately 50% and 75% of the expected EFS events.

The data cut-off for the first planned interim analysis (approximately 50% information fraction) was December 31, 2023. The Applicant reported that at this analysis, the futility monitoring bound was crossed, and Arm B was closed as of March 5, 2024. No information from the first planned interim analysis was included in this supplement or the referenced IND. The Applicant provided ad hoc analyses of data as of January 28, 2025, which included participants accrued to Arms A and B through March 2024 when Arm B was closed.

The analysis population included 724 participants (361 in Arm A and 363 in Arm B). The VYXEOS arm included 324 pediatric patients less than 17 years old. The Applicant reported an EFS HR of 1.39 (95% CI: 1.09-1.77) and an OS HR of 1.08 (95% CI: 0.78-1.48). This was a negative trial. Among the EFS events, the number of induction failures, number of relapses, and number of deaths were all higher in the VYXEOS arm. Among the safety outcomes, the median times to neutrophil and platelet recovery were longer in the VYXEOS arm.

In accordance with 505B(g)(2) of the FD&C Act, the review team recommended stating in USPI Section 8.4 that the safety and effectiveness of Vyxeos were not established for first-line treatment of de novo AML. Although the results of the Study AAML1831 were not sufficient to determine a safe and effective dose of Vyxeos and GO to support an indication, the Division concluded that, technically, the terms of the PWR were met. The details of the Division's evaluation of the Applicant's response to the PWR are provided in a separate review.[1]

[1] NDA 209401 Pediatric Exclusivity Determination Checklist dated 1/9/2026.

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1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

X	Patient experience data was not submitted as part of this application.

2 THERAPEUTIC CONTEXT

2.1 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. AML is universally fatal without treatment.

According to the National Cancer Institute's SEER database[2], it is estimated that there were 22,010 new cases of AML in 2025, and 11,090 deaths from AML. Pediatric AML is rare, making up less than 4% of the total new cases of AML. It accounts for 15-20% of childhood leukemias, affecting about 8 children per million annually[3]. The highest incidence is in infants under one year old and decreases with age before increasing slightly in adolescents. Minimal variability is observed by race or ethnicity in the United States[4]. The overall 5-year survival rate for children with AML is 65-70%. Outcomes are influenced by multiple factors including risk group based on cytogenetic and/or molecular genetic alterations and response to initial treatment.

2.2 Analysis of Current Treatment Options

Table 1 shows the approved therapies for first-line treatment of de novo AML. The only cytotoxic drugs approved for first-line treatment for pediatric patients with AML that are currently in use include combination of daunorubicin and cytarabine with or without gemtuzumab ozogamicin.

[2] SEER Cancer Statistics Facts Sheet – Acute Myeloid Leukemia (AML) https://seer.cancer.gov/statfacts/html/amyl.html , Accessed December 31, 2025
[3] NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. National Cancer Institute; 2025 Sep 24. [cited 2025 Dec 31]. Available from: https://nccrexplorer.ccdi.cancer.gov.
[4] Siegel, David A et al. "Counts, incidence rates, and trends of pediatric cancer in the United States, 2003-2019." Journal of the National Cancer Institute vol. 115,11 (2023): 1337-1354. doi:10.1093/jnci/djad115

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Table 1. Available Therapy for First-Line Treatment of AML

Agent	Excerpted Indication
Cyclophosphamide	Cyclophosphamide For treatment of acute myelogenous and monocytic leukemia, most frequently concurrently or sequentially with other antineoplastic drugs
Cytarabine	In combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults and children.
Daunorubicin	In combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Doxorubicin	For treatment of acute myeloblastic leukemia
Gemtuzumab	For treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults and pediatric patients 1 month and older; and for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and pediatric patients 2 years and older.
Glasdegib	In combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy
Idarubicin	In combination with other approved anti-leukemic drugs for treatment of AML in adults
Ivosidenib	In combination with azacitidine or as monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
Midostaurin	In combination with cytarabine and daunorubicin induction and cytarabine consolidation in adults with newly-diagnosed AML that is FLT3 mutation-positive as detected by an FDA approved test.
Mitoxantrone	In combination with other approved drugs in the initial therapy of acute nonlymphocytic leukemia in adults
Quizartinib	In combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test
Thioguanine	For remission induction and consolidation treatment of acute non-lymphocytic leukemia.
Venetoclax	In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Vincristine	In acute leukemia
(Daunorubicin and cytarabine) liposome	For the treatment of newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older

3 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

Vyxeos (CPX-351) was approved on August 3, 2017 for the treatment of adults with newly-diagnosed t-AML or AML-MRC. On March 30, 2021, the approved indication was expanded to include pediatric patients 1 year and older.

3.2 Summary of Presubmission/Submission Regulatory Activity

Presubmission interactions with the Applicant were conducted under IND 072939.

- August 28, 2020 – FDA issued a pediatric Written Request to obtain data to support efficacy and safety of Vyxeos in the pediatric population; the PWR included 3 studies: AAML1421, CPX-MA-1201, AAML1831)

- October 7, 2020 – NDA 209401 S-006 submitted to expand the approved adult indication to include pediatric patients 1 year and older based on AAML1421 and CPX-MA-1201 (Studies 1 and 2 from the PWR)

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 Office of Scientific Investigations (OSI)

The clinical data in this supplement are from a negative clinical trial. Because the Applicant is not making an efficacy claim, no clinical site inspections were requested.

4.2. Product Quality

There was no new product quality information submitted in this supplement.

4.3 Devices and Companion Diagnostic Issues

There is no proposed companion or complementary diagnostic for the new intended population.

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5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There were no new nonclinical data submitted in this supplement.

6 CLINICAL PHARMACOLOGY

6.1 Executive Summary

Vyxeos (CPX-351) is a liposomal formulation containing daunorubicin and cytarabine in a fixed 1:5 molar ratio. It was initially approved in August 2017 for treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). The recommended initial dose was (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome days 1, 3 and 5.

A Written Request (PWR) was issued to investigate the potential use of Vyxeos in the treatment of AML in pediatric patients 1 to < 17 years old in three studies (Study 1, 2 and 3). The indication was expanded in March 2021 in pediatric patients ≥ 1 year old with the same indications based on the results from Study 1 and Study 2. The recommended dosing regimen in pediatric patients is identical to the previously approved regimen in adults.

Study 3 (AAML1831) was a Phase 3 randomized trial in pediatric patients (< 22 years of age) with de novo AML comparing Arm A (standard therapy daunorubicin + cytarabine) + gemtuzumab ozogamicin to Arm B (CPX-351 + gemtuzumab ozogamicin) with event-free survival (EFS) as the primary endpoint. Arm B enrollment was halted, because the futility monitoring threshold was crossed and the primary objective was unlikely to be achieved.

Arm B dosing regimen was as below:

- BSA ≥ 0.6 m^2: 60 mg/m^2/dose daunorubicin (~135 mg/m^2/dose cytarabine)
- BSA < 0.6 m^2: 2 mg/kg/dose daunorubicin (~4.5 mg/kg/dose cytarabine)

The Clinical Pharmacology results included PK Analysis from 42 participants in Arm B (Induction 1) had evaluable PK data. Exposure was consistent with adult and previous pediatric studies (Study 1 and 2).

For the current submission, the Applicant proposed to add data from Study AAML1831 to USPI Section 8.4 (Pediatric Use) per Written Request requirements. While there was no new information on PK from a Clinical Pharmacology perspective, the following sentence from

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Section 12.3 in the currently approved labeling was added to Section 8.4 based on the overall PK information available in pediatrics as compared to the adults, "The exposures of total daunorubicin and cytarabine observed in pediatric patients were within the values observed in adults given the same dose based on body surface area".

7 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1 Table of Clinical Studies

Table 2. Clinical Trials of CPX-351

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries
AAML1831	Phase 3 randomized trial study of CPX-351 vs DA with GO Primary endpoint: EFS	Arm A: DA+GO Arm B: CPX-351+GO Induction 1 - CPX 60 mg/m^2 days 1, 3, 5 Induction 2 - CPX 50 mg/m^2 days 1, 3, 5	n = 724 Age: 1-21 years de Novo AML	US: 146 Canada: 14 Australia: 1

Source: FDA analysis

7.2 Review Strategy

The key materials used for the review of efficacy and safety included:

- sNDA dataset, clinical study reports, case report forms, and responses to the review team's IRs
- FDA Review of NDA 209401 and prior supplements
- Relevant published literature
- Relevant information in the public domain

Table 3. sNDA Submission and Amendments

eCTD SDN	Received	Category	Subcategory
578	7/30/2025	New	Supplement
585	9/26/2025	Clinical	Response to Information Request (revised ADAE, safety analyses)
591	11/4/2025	Clinical	Response to Information Request (efficacy data collection, analyses)

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The Applicant submitted information from AAML1831 for the assessment of efficacy and safety of CPX-351 for the treatment of newly diagnosed de novo AML. The trial was terminated for futility at a planned interim analysis and is considered a negative study. Therefore, additional efficacy analyses were not conducted, and the Applicant's reported findings were not independently adjudicated by FDA. The efficacy analyses in the review below are based solely on the Applicant-submitted CSR and responses to information requests.

8 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 AAML1831

AAML1831

INVESTIGATIONAL PLAN

Trial Design and Endpoints

Study AAML1831 (NCT04293562) included an open-label randomized comparison of Vyxeos plus gemtuzumab ozogamicin (GO) to standard chemotherapy plus GO in pediatric patients with de novo AML without a FLT3 mutation. Eligible patients were randomized 1:1 to receive 2 cycles of induction using standard daunorubicin + cytarabine + GO (Arm A) or CPX 351 + GO (Arm B) (see figure below). Randomization was stratified by risk group (Low Risk 1, Low Risk 2, High Risk). The primary objective was to compare event-free survival (EFS) between Arms A and B. A secondary objective was to compare overall survival (OS) between Arms A and B. Per the SAP and the protocol for Study AAML1831, patients were to be randomized 1:1 during initial study enrollment to Arm A (Daunorubicin + Cytarabine + GO) or Arm B (CPX-351 + GO) (1:1 randomization ratio).

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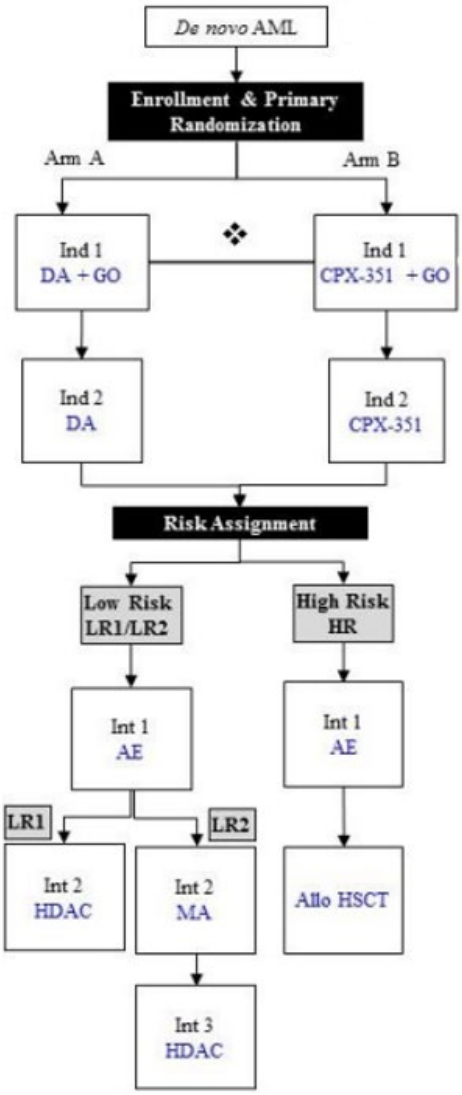
Figure 1 Study AAML1831 Schema for Arms A and B



Source: Excerpted from AAML1831 Protocol Experimental Design Schema

Key Eligibility

- This study included pediatric participants (< 22 years of age) who had newly diagnosed de novo AML according to 2016 WHO classification with or without extramedullary disease.

Treatment Plan

Induction (2 cycles)

- Arm A (DA-GO))
    - Induction 1: standard 7+3 daunorubicin + cytarabine (DA) + gemtuzumab ozogamicin (GO) on Day 6

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  - Induction 2: 7+3 DA
- Arm B (CPX-351-GO)
  - Induction 1: CPX-351 IV 60 mg/m^2/dose (or 2 mg/kg/dose if BSA < 0.6 m^2) of daunorubicin on Days 1, 3, and 5 + GO on Day 6
  - Induction 2: CPX-351 IV 50 mg/m^2/dose (or 1.7 mg/kg/dose if BSA < 0.6 m^2) of daunorubicin on Days 1, 3, and 5
- The Induction 1 dose of GO was the same in Arm A and Arm B

Post-induction treatment was the same for all participants based on risk stratification (LR1 vs LR2 vs HR) using results of cytogenetics, molecular diagnostics, transcriptome sequencing, and end induction flow cytometry.

Primary endpoint
- Event-free survival (EFS)

Secondary endpoint
- Overall survival (OS)

Statistical Analysis Plan

Analysis Populations
- Intent-to-Treat (ITT) Analysis Set: All enrolled patients without FLT3 mutation randomized to Arm A and Arm B. This is the primary analysis set for efficacy data, analyzed according to randomized treatment assignment regardless of treatment actually received.
- Safety (All Treated) Analysis Set: All enrolled patients without FLT3 mutation randomized to Arm A and Arm B who received at least one dose of study treatment.

Efficacy Analysis

Primary Efficacy Endpoint: Event-Free Survival (EFS)
Definition: Time (months) from randomization to first event (induction failure, relapse, second malignant neoplasm, or death) or censored at date of last contact for those who are event-free.

Analysis Method:

- Kaplan-Meier method for EFS estimation with Greenwood standard errors (EFS estimates with the corresponding 95% CIs at landmarks: 3, 6, 12, 18, and 24 months)
- Log-rank test to compare treatment arms (two-sided significance level 0.05, adjusted for interim analyses). The protocol did not explicitly state whether this test was to be stratified or unstratified.
- Cox proportional hazards model for hazard ratio with 95% CI

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Sensitivity Analysis: Restricted mean survival time if the proportional hazards assumption was violated.

Key Secondary Efficacy Endpoint: Overall Survival (OS)
Definition: Time (months) from randomization to death or censored at date of last contact for those alive at last contact.

Analysis Method:

- Kaplan-Meier method with Greenwood standard errors (OS estimates with the corresponding 95% CIs at landmarks: 3, 6, 12, 18, and 24 months)
- Log-rank test to compare treatment arms
- Cox proportional hazards model for hazard ratio with 95% CI
- OS comparison performed only if significant difference found on EFS analysis

Sample Size and Power
With approximately 534 patients without FLT3 mutations on Arm A and Arm B each, this study was planned to have at least 80% power using 2-sided log- rank test with 0.05 type I error to detect an EFS hazard ratio of 0.762 which corresponds to an 8.4% difference in 5-year EFS (54.8% vs 63.2%). Under the alternative hypothesis, 428 events were expected to occur by 2 years of follow-up.

Interim Analyses
Interim analyses to assess efficacy and futility of Arms A and B were planned at approximately 50% and approximately 75% of the expected information based on Lan-DeMets criterion with α-spending function and 2.5% type I error. For futility monitoring, lower boundaries based on testing the alternative hypothesis at the 0.024 level using the approach of Anderson and High were to be used. If the boundary for futility was crossed at an interim analysis, Arms A and B of the study were planned to stop.

Key Protocol Amendments
AAML1831 underwent 5 protocol amendments as of the data cutoff date for this sNDA. There were no major protocol amendments that impacted the conduct of Arms A and B of the study.

STUDY RESULTS

Compliance with Good Clinical Practices
The Applicant stated in Module 2.5 and in the Clinical Study Report in the synopsis and Ethics section that the trial was conducted in accordance with Good Clinical Practice (GCP) guidelines,

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the Declaration of Helsinki, and standard operating procedures for clinical research and development at COG.

Financial Disclosure

There were 3,160 investigators/sub-investigators who participated in AAML1831. Sixty-six investigators/sub-investigators reported a possible financial conflict of interest with either Jazz Pharmaceuticals or (b) (4). according to information submitted to CTEP. Form 3455 was submitted for these investigators, but the Applicant was unable to obtain information on disclosable financial arrangements and interests since CTEP does not provide Financial Disclosure Forms to external parties. There is no description of a search based on the Applicant's databases. However, AAML1831 was a large, randomized study conducted across 161 sites and no single site enrolled more than 3.5% of study participants. Therefore, it is unlikely that the data from any one site or investigator would bias overall study conclusions. Additionally, AAML1831 is a negative study and would not be sufficient to establish the efficacy of CPX-351 in support of a new indication. A Form 3454 was submitted for attestation of no financial conflict of interest for the remainder of the Investigators.

Data Quality and Integrity

Several data quality issues were identified during review of the efficacy data submitted in this application. The primary endpoint of the study was EFS. However, the dataset did not appear to include a variable for date of remission. Additionally, the EFS event date for induction failure and relapse was described as "reporting period end date" rather than an actual date of the event. In the response to IR (SDN 591), the Applicant stated that data on response were not collected in the CRF and therefore no actual remission date could be assigned. The date of induction failure was described as the last date of the treatment cycle in which induction failure occurred, and the relapse date reflected the actual relapse date for some participants or the last date of the treatment cycle during which relapse occurred if the actual date was not available. These issues with data collection and quality preclude reliable conduct of additional efficacy analyses by FDA. However, AAML1831 was a large, randomized trial that was terminated early for futility. The study would therefore not be appropriate to support any efficacy claims in labeling. FDA's review below will rely on the information in the Applicant's CSR to describe the comparative efficacy outcomes at the time of the interim analysis and any observed differences between treatment arms.

Patient Disposition

- First subject screened – 21 July 2020
- Enrollment to AAML1831 Arm B was closed permanently as of 05 March 2024
- Primary database cutoff – 28 January 2025

At the time of database closure, 67% of participants remained on protocol therapy.

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Table 4. AAML1831 – Patient Disposition

	Arm A (DA-GO) N = 361	Arm B (CPX-351-GO) N = 363	Overall N = 724
Received at least 1 dose of study treatment, n (%)	357 (98.9)	361 (99.4)	718 (99.2)
Completed protocol therapy, n (%)	226 (62.6)	194 (53.4)	420 (58.0)
Off protocol therapy, n (%)	101 (28.0)	135 (37.2)	236 (32.6)
Reason off protocol therapy			
• Failure to achieve CR at end of Induction 2	16 (4.4)	20 (5.5)	36 (5.0)
• Relapse	15 (4.2)	24 (6.6)	18 (2.5)
• Other	70 (19.3)	91 (25.0)	182 (25.1)
Completed study, n (%)	0	0	0
Discontinued study, n (%)	26 (7.2)	27 (7.4)	53 (7.3)
Reason for discontinuing study			
• Death	14 (3.9)	14 (3.9)	28 (3.9)
• Other	12 (3.3)	13 (3.6)	25 (3.4)

Source: Excerpted from AAML1831 CSR Table 1

Protocol Violations/Deviations

According to Section 4.2 of the AAML1831 CSR:
"As per COG policy, protocol deviations that were made in the interest of participant management were not subject to review and interpretation by a physician auditor (e.g., COG study chair). The physician responsible for the participant's management and care was stipulated to be the only individual authorized to decide if the participant should be removed from protocol therapy. COG reviewed participant eligibility criteria and identified participants who were an eligibility deviation at the time of study entry (ineligible) or at the time of randomization (not evaluable)."

Four (1.1%) participants in Arm A and two (0.6%) in Arm B were discontinued from the study prior to start of treatment due to an excluded constitutional condition or oncologic diagnosis identified after enrollment (AAML1831 CSR Section 4.1). No other information on protocol deviations is included in the CSR.

Table of Demographic Characteristics

The Applicant's CSR describes the demographics and baseline characteristics of the treated population (n = 718) rather than the ITT population (n = 724). The 6 patients omitted from the ITT population (see Protocol Deviations) would not be expected to substantively alter the composition of the study population in either arm, so the Applicant's analyses of demographics and baseline disease characteristics in the treated population are shown below.

The two treatment arms were generally balanced with respect to baseline demographics. Of the 718 treated patients, the median age was 10 years (range: 0.003 to 21 years); 56% were male; 63% were White, 9.6% were Black or African American, 4.9% were Asian and 22.5% were

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other races or unknown race.

Table 5. AAML1831 – Demographics (Treated Population)

	DA-GO (Arm A) (N=357)	CPX-351-GO (Arm B) (N=361)	Overall (N=718)
Age at Enrollment (years)			
n	357	361	718
Mean (SD)	9.4 (6.24)	8.9 (6.41)	9.2 (6.32)
Median	10.0	9.0	10.0
Q1, Q3	3.0, 15.0	2.0, 15.0	3.0, 15.0
Min, Max	0.058, 21	0.003, 21	0.003, 21
Age Group, n (%)			
< 2 years	60 (16.8)	75 (20.8)	135 (18.8)
2 to < 6 years	56 (15.7)	61 (16.9)	117 (16.3)
6 to < 12 years	92 (25.8)	75 (20.8)	167 (23.3)
12 to < 16 years	73 (20.4)	77 (21.3)	150 (20.9)
≥ 16 years	76 (21.3)	73 (20.2)	149 (20.8)
Sex at Birth, n (%)			
Female	158 (44.3)	155 (42.9)	313 (43.6)
Male	199 (55.7)	206 (57.1)	405 (56.4)
Race, n (%)			
American Indian or Alaska Native	6 (1.7)	6 (1.7)	12 (1.7)
Asian	17 (4.8)	18 (5.0)	35 (4.9)
Black or African American	30 (8.4)	39 (10.8)	69 (9.6)
Multiple Races	4 (1.1)	4 (1.1)	8 (1.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.1)
White	240 (67.2)	214 (59.3)	454 (63.2)
Unknown	59 (16.5)	80 (22.2)	139 (19.4)
Ethnicity, n (%)			
Hispanic or Latino	89 (24.9)	84 (23.3)	173 (24.1)
Not Hispanic or Latino	231 (64.7)	236 (65.4)	467 (65.0)
Unknown	37 (10.4)	41 (11.4)	78 (10.9)

Source: AAML1831 CSR Table 3

Other Baseline Characteristics

The two treatment arms were generally balanced with respect to baseline disease characteristics as shown in Table 6.

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Table 6. AAML1831 – Baseline Disease Characteristics (Treated Population)

	Arm A (DA-GO) N = 357	Arm B (CPX-351-GO) N = 361	Overall N = 718
CNS status at baseline			
- CNS 1 (negative)	103 (28.9)	92 (25.5)	195 (27.2)
- CNS 2	17 (4.8)	14 (3.9)	31 (4.3)
- CNS 3	22 (6.1)	23 (6.4)	45 (6.3)
Genetic abnormalities			
- t(9;11) KMT2A	28 (7.8)	31 (8.6)	59 (8.2)
- Any KMT2A fusion or partial tandem duplication	22 (6.2)	18 (5.0)	40 (5.6)
- Inv(16) CBFA2T3-GLIS2	5 (1.4)	4 (1.1)	9 (1.3)
- t(7;12) MNX1-ETV6	3 (0.8)	1 (0.3)	4 (0.6)
- t(11;12) NUP98	1 (0.3)	1 (0.3)	2 (0.3)
- t(6;9) DEK-NUP214	1 (0.3)	1 (0.3)	2 (0.3)

Source: Excerpted from AAML1831 CSR Table 4

Treatment Compliance

Study intervention administration was performed by study site staff at the site. Three (0.8%) participants in Arm B had at least 1 dose missed during Induction 1 due to "other" reason. No participants in Arm B had any dose missed during Induction 2.

Efficacy Results – Primary Endpoint

Table 7 shows summary of event-free survival by treatment arms using ITT population. The median EFS was not estimable for Arm A and was estimated as 30.9 months (95% CI, 20.9-NC) for Arm B. The estimated hazard ratio (95% CI) was 1.39 (1.09-1.77) with a p-value of 0.008. The most common event in EFS was relapse, which occurred in 78 (21.6%) participants in Arm A and 102 (28.1%) participants in Arm B. Figure 2 shows Kaplan-Meier plot of event-free survival using ITT population.

Table 7. Event-Free Survival – ITT Analysis Set

	DA-GO (Arm A) (N=361)	CPX-351-GO (Arm B) (N=363)
EFS, n (%)		
Number of Events	114 (31.6)	151 (41.6)
Induction Failure	17 (4.7)	24 (6.6)
Relapse	78 (21.6)	102 (28.1)
Death	19 (5.3)	25 (6.9)
Number Censored	247 (68.4)	212 (58.4)
EFS Time (Months)[a]		
Q1 (95% CI)	12.0 (10.0-14.2)	8.9 (7.8-10.6)
Median (95% CI)	NC (NC-NC)	30.9 (20.9-NC)

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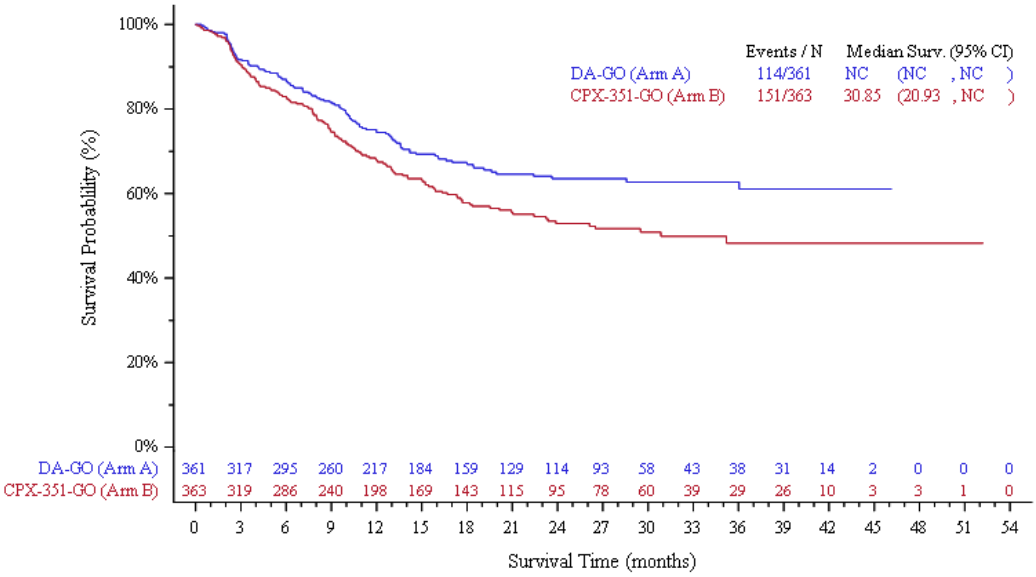
Q3 (95% CI)	NC (NC-NC)	NC (NC-NC)
EFS Rate (95% CI) at[a]		
3 Months	0.92 (0.89-0.95)	0.90 (0.87-0.93)
6 Months	0.87 (0.84-0.91)	0.83 (0.79-0.87)
12 Months	0.74 (0.70-0.79)	0.68 (0.63-0.73)
18 Months	0.67 (0.62-0.72)	0.58 (0.52-0.63)
24 Months	0.64 (0.58-0.69)	0.53 (0.47-0.59)
Hazard Ratio[b]		
Estimate (95% CI)		1.39 (1.09-1.77)
p-value		0.008
Abbreviations: CPX-351-GO = induction therapy with CPX-351 and GO; DA = daunorubicin, cytarabine; DA-GO = standard induction therapy with daunorubicin, cytarabine (DA), and GO; EFS = event-free survival; GO = gemtuzumab ozogamicin; ITT = intent to treat; NC = not calculable; Q1 = first quartile; Q3 = third quartile. [a] Confidence intervals estimated using the Brookmeyer-Crowley method. [b] Hazard ratios and the two-sided p-value were estimated using the unstratified log-rank test and Cox proportional hazards model.		

Source: Excerpted from AAML1831 CSR Table 6.

Figure 2. Kaplan-Meier Plot of Event-Free Survival – ITT Analysis Set



Source: Excerpted from AAML1831 CSR Figure 2.

Efficacy Results – Secondary and Other Relevant Endpoints

Table 8 shows summary of the key secondary endpoint overall survival by treatment arms using ITT population. The median OS was not estimable for both arms. The estimated hazard ratio (95% CI) was 1.08 (0.78-1.48) with a p-value of 0.651. Figure 3 shows Kaplan-Meier plot of

overall survival using ITT population.

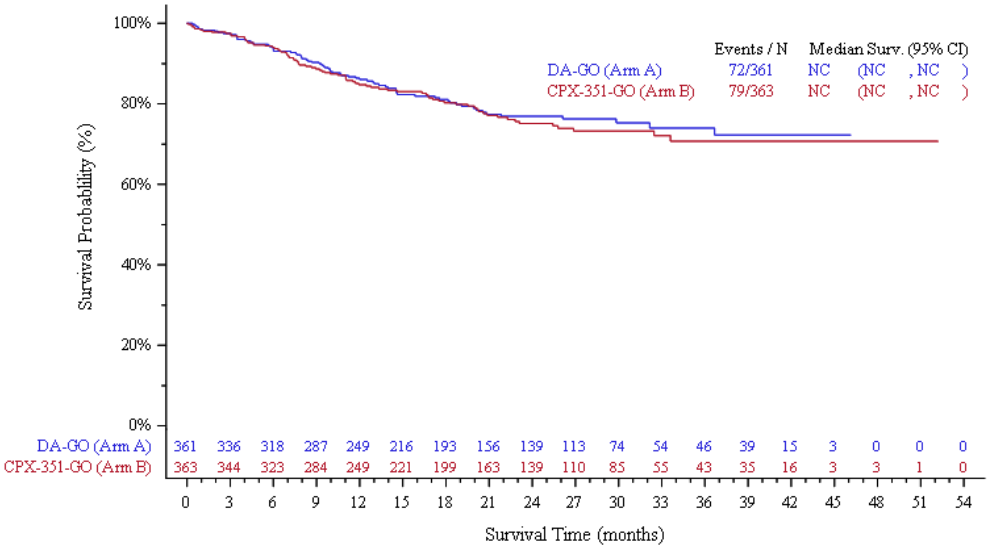
Table 8. Overall Survival - ITT Analysis Set

	DA-GO (Arm A) (N=361)	CPX-351-GO (Arm B) (N=363)
OS, n (%)		
Number of Deaths	72 (19.9)	79 (21.8)
Number Censored	289 (80.1)	284 (78.2)
OS Time (Months)[a]		
Q1 (95% CI)	32.2 (19.1-NC)	25.4 (19.5-NC)
Median (95% CI)	NC (NC-NC)	NC (NC-NC)
Q3 (95% CI)	NC (NC-NC)	NC (NC-NC)
OS Rate (95% CI) at[a]		
3 Months	0.97 (0.96-0.99)	0.97 (0.96-0.99)
6 Months	0.94 (0.91-0.96)	0.94 (0.92-0.97)
12 Months	0.86 (0.82-0.90)	0.85 (0.81-0.89)
18 Months	0.81 (0.77-0.85)	0.80 (0.76-0.85)
24 Months	0.77 (0.72-0.82)	0.75 (0.70-0.80)
Hazard Ratio[b]		
Estimate (95% CI)	1.08 (0.78-1.48)	
p-value	0.651	

Abbreviations: CPX-351-GO = induction therapy with CPX-351 and GO; DA = daunorubicin, cytarabine; DA-GO = standard induction therapy with daunorubicin, cytarabine (DA), and GO; GO = gemtuzumab ozogamicin; ITT = intent to treat; NC = not calculable; OS = overall survival; Q1 = first quartile; Q3 = third quartile.
[a] Confidence intervals estimated using the Brookmeyer-Crowley method.
[b] Hazard ratios and p-values were estimated using the Cox proportional hazards model.

Source: Excerpted from AAML1831 CSR Table 7.

Figure 3. Kaplan-Meier Plot of Overall Survival – ITT Analysis Set



Source: Excerpted from AAML1831 CSR Figure 3.

Reviewer's Comment:
The first planned interim analysis occurred at approximately 50% of events (data cutoff: 31 December 2023). The futility monitoring rule was crossed. As of 05 March 2024, enrollment to Arms A and B was closed; Arm B was permanently closed, and Arm A was subsequently reopened on 28 April 2025.

All data reported are based on a data cutoff date of 28 January 2025, which includes additional participants accrued between the 31 December 2023 IA trigger and closure of accrual to Arms A and B in March 2024. The ITT Analysis Set based on the final dataset consisted of 724 participants (361 participants in Arm A and 363 participants in Arm B). All p-values presented are nominal and for descriptive purposes only.

8.2 Integrated Review of Effectiveness

Methods: The Applicant proposed no new indications and no new intended population. In this supplement, the Applicant submitted one trial, Study AAML1831, in support of a labeling revision in Section 8.4 of the USPI. AAML1831 is an open-label randomized trial comparing CPX-351 plus GO to standard chemotherapy (DA) plus GO in pediatric patients with de novo AML without a FLT3 mutation. The primary endpoint was EFS.

Primary Efficacy Endpoint: The primary endpoint was EFS, but the Applicant's definition of EFS (events: induction failure, relapse, second malignant neoplasm, or death) is not consistent with the EFS definition used for regulatory actions.

The study design included preplanned interim analyses at approximately 50% and 75% of the expected information based on Lan-DeMets criterion. The Applicant reported that at the first interim analysis (December 31, 2023), the futility monitoring bound was crossed. Arm B was closed as of March 5, 2024. Ad hoc analyses were provided based on data from participants enrolled to Arms A and B through March 2024 with a data cutoff of January 28, 2025. The analysis population included a total of 724 participants, 361 in Arm A and 363 in Arm B. The Applicant reported EFS HR of 1.39 (95% CI: 1.09-1.77). EFS events of induction failure, relapse, and death all occurred in a higher proportion of participants in the CPX-351 arm. The Applicant concluded that the efficacy of CPX-351 had not been established for the study population. The review team agrees with this conclusion but notes that the results fulfill the EFS reporting requirement of the PWR.

Integrated Assessment of Efficacy:
AAML1831 was a negative study that was terminated for futility at a preplanned interim analysis. Therefore, the efficacy of CPX-351 for treatment of newly diagnosed de novo AML has not been established. However, the submission fulfills the study design, objectives, enrollment, treatment, and statistical requirements of the PWR.

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8.3 Review of Safety

8.3.1. Safety Review Approach

FDA's review of safety for this sNDA focused on data from AAML1831. The safety population for AAML1831 was comprised of 716 participants including 357 participants in Arm A (DA-GO) and 361 participants in Arm B (CPX-351-GO) who received at least one dose of study drug as of the data cutoff of 28 January 2025.

The safety review relied upon data and analyses provided in an updated ADAE date file submitted in eCTD 585 and responses to IR (see discussion regarding data integrity below). The clinical reviewer conducted additional high-level analyses of adverse events of special interest not adequately addressed in the CSR or responses to IR. These analyses were performed using SAS/JMP 17.2.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) version 4.5.1. (FDA, Silver Spring, MD). Because CPX-351 and DA were given only during Induction cycles 1 and 2 and the remainder of treatment on study was the same in both arms, the analyses of safety discussed below focus on adverse events occurring in Induction Cycles 1 and 2 in order to address the issue of the toxicity of CPX-351.

Anticipated Safety Issues
The known safety risks of treatment with CPX-351 include:

- Hemorrhage
- Cardiotoxicity
- Hypersensitivity reactions
- Copper overload

Demographics of the Safety Population
See Table 5 and Table 6 in Section 8.1.1. Overall, the demographics of the safety population are consistent with those expected of pediatric patients in the United States with newly diagnosed AML.

Adequacy of the Safety Database
The size of the safety database is adequate to identify common acute toxicities.

Issues Regarding Data Integrity and Submission Quality
Numerous issues were identified with the ADAE data file included in the original sNDA submission. It was unclear from the define file what coding dictionary had been used for mapping investigator verbatim terms to preferred terms in the adverse event data files. Furthermore, the AE and ADAE data files included many general HLGT classifications instead of specific AE terms which were not consistent with MedDRA preferred term values. In addition, the AEDECOD parameter in ADAE did not appear to be a reliable coding of the terms reported in AETERM. Specifically:

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- Multiple verbatim terms (AETERM) were coded incorrectly in AEDECOD.
- Some identical verbatim terms had more than one corresponding AEDECOD.
- Some similar verbatim terms were coded differently.
- Multiple verbatim terms including, but not limited to, "Blood" or "Mouth" were coded as "Infections and infestations – Other, specify." It was unclear whether the AETERMS were entered incompletely into the data file or how AEDECOD was derived for these incomplete terms.

An IR was sent to the Applicant requesting clarification on the coding dictionary used to construct the AE data files and the methodology used to derive AEDECOD from the AETERM. The Applicant indicated that the data provided to them by Children's Oncology Group (COG) did not include MedDRA coding. Adverse events were coded by the Applicant using CTCAE v5.0 verbatim terms but entry of a MedDRA version was required when converting raw data into SDTM format. This approach resulted in inconsistencies, including incomplete or abbreviated verbatim terms that did not map appropriately and, in some cases, led to incorrect categorization. The Applicant corrected and re-mapped all AETERMS to MedDRA version 27.0 and submitted a revised ADAE data file in SDN 585. This data file was used by FDA for independent analysis of adverse events of special interest. The submission also included updated safety analyses based on the revised data file. However, the analyses provided reflected data inclusive of all time on study. Since CPX-351 and DA were given only during Induction cycles 1 and 2, these analyses were not appropriate to address the toxicity of CPX-351. FDA requested additional comparative safety analyses restricted to Induction cycles 1 and 2. The Applicant provided these analyses in SDN 591.

Categorization of Adverse Events
Adverse events, PTs, and event severity were coded using CTCAE, version 5.0.

Routine Clinical Tests
Routine laboratory monitoring of hematology, electrolytes, blood chemistry, and urine and regular assessments of vital signs and physical condition were performed by investigators for monitoring the safety of all participants but were not collected as part of the study data. These routine laboratory assessments were recorded in the participants' medical records. These results included physical examinations, electrolytes, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, and blood biomarkers. Therefore, these results are not included or discussed in this CSR. Adverse events identified from laboratory procedures and assessments were to be reported on the AE CRF.

8.3.2. Safety Results

Exposure
Exposure data were collected only for Arm B. A majority of patients received all planned doses of CPX-351 with <1% missing at least 1 dose and <1% requiring dose modification.

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- Induction 1
  - Cumulative total dose: median 180 mg/m^2 (range: 39, 207)
  - Missed at least one dose: 3 (0.8%)
    - Reasons: other NOS (n = 3)
  - At least one dose modification: 3 (0.8%)
    - Reasons: toxicity (n = 1), other NOS (n = 2)
- Induction 2
  - Cumulative total dose: median 150 mg/m^2 (range: 143.7, 180.0)
  - Missed at least one dose: 0
  - At least one dose modification: 0

Deaths

There was a higher number of deaths in Arm B compared to Arm A over the course of the study and in Induction 2, though the incidence of early mortality was low in both arms.

Table 9. AAML1831 – Deaths

	Arm A (DA-GO) N = 361	**Arm B (CPX-351-GO) N = 357**
Deaths Overall, n (%)	72 (20.2)	79 (21.9)
Applicant-Reported Primary Cause of Death		
• Treatment, n (%)	4 (1.1)	1 (0.3)
• Disease, n (%)	51 (14.3)	56 (15.5)
• Other, NOS, n (%)	17 (4.8)	22 (6.1)
Induction 1, n (%)	6 (1.7)	5 (1.4)
Applicant-Reported Primary Cause of Death		
• Treatment, n (%)	0	0
• Disease, n (%)	3 (0.8)	2 (0.6)
• Other, NOS, n (%)	3 (0.8)	3 (0.8)
Induction 2, n (%)	2 (0.6)	4 (1.1)
Applicant-Reported Primary Cause of Death		
• Treatment, n (%)	1 (0.3)	0
• Disease, n (%)	1 (0.3)	1 (0.3)
• Other, NOS, n (%)	0	3 (0.8)

Source: Excerpted from AAML1831 CSR Table 18

Treatment-Emergent Adverse Events (TEAE) during Induction 1 and 2

Common TEAEs that occurred during the 2 cycles of induction are shown in Table 10. The type and severity of TEAEs was generally similar between arms with the exception of a substantially higher incidence of hypertension and rash in Arm B compared to Arm A.

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Table 10. AAML1831 – Common TEAEs (≥ 10% in Arm B) During Induction Cycles 1 and 2

TEAE/Preferred Term (PT)*	All Grades		Grades 3 or Higher	
	Arm A (DA-GO) N=357 n (%)	Arm B (CPX-351-GO) N=361 n (%)	Arm A (DA-GO) N=357 n (%)	Arm B (CPX-351-GO) N=361 n (%)
Febrile neutropenia	159 (44.5)	191 (52.9)	159 (44.5)	191 (52.9)
Hypertension	34 (9.5)	90 (24.9)	34 (9.5)	87 (24.1)
Sepsis	43 (12.0)	71 (19.7)	43 (12.0)	71 (19.7)
Decreased appetite	42 (11.8)	62 (17.2)	42 (11.8)	62 (17.2)
Rash maculo-papular	7 (2.0)	62 (17.2)	7 (2.0)	59 (16.3)
Alanine aminotransferase increased	41 (11.5)	61 (16.9)	41 (11.5)	61 (16.9)
Ejection fraction decreased	56 (15.7)	56 (15.5)	5 (1.4)	16 (4.4)
Hypokalaemia	42 (11.8)	51 (14.1)	42 (11.8)	51 (14.1)
Stomatitis	23 (6.4)	48 (13.3)	23 (6.4)	48 (13.3)
Aspartate aminotransferase increased	46 (12.9)	47 (13.0)	46 (12.9)	47 (13.0)

*Graded per CTCAE version 5.
Source: Applicant Response to IR 11/4/2025 (SEQ 0591)

In contrast to the CSR which reported similar cumulative rates of infection between arms over the full study (induction through intensification and follow-up), FDA's analysis showed that infections were significantly more common in Arm B during Induction Cycles 1 and 2.

- SOC Infections and infestations: 19.9% in Arm B compared to 31.1% in Arm B (all reported events were Grade ≥ 3 events)

- The vast majority of events were classified as HLGT Infections – pathogen unspecified – 19.3% vs 30.2%, respectively.

<u>Adverse Events of Special Interest during Induction Cycles 1 and 2</u>

- Hemorrhage –
  - FDA grouped term: Broad SMQ Haemorrhage terms (excl laboratory terms)
  - Hemorrhage (all reported events were Grade 3 or 4): 9 (2.5%) vs 30 (8.3%) in Arm A vs Arm B, respectively.
  - The most common hemorrhage AE was epistaxis in both arms (1.6% vs 6.6%).

- Cardiotoxicity –
  - The Applicant reported that no remarkable mean changes from baseline in ECG parameters (QT interval, heart rate) or ECHO parameters (shortening fraction, EF) were observed at any visit or overall in either arm.

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  - FDA grouped term: SOC Cardiac disorders
    - The overall incidence of cardiac disorders was low at 1.4% and 3.9% of participants in Arm A and Arm B, respectively.

- Hypersensitivity –
  - FDA grouped term: SMQ Hypersensitivity (broad and narrow search = Y)
  - Hypersensitivity: 10 (2.3%) vs 65 (18%) in Arm A and Arm B, respectively
    - Grade 3 rash accounted for the majority of events reported in participants in both arms (2% vs 17%, respectively)
    - Two (0.5%) participants on each arm were reported to have had an infusion-related reaction event – in Arm A the events were Grade 2 and Grade 3; in Arm B the events were Grade 3 and Grade 4

- Copper overload – Copper levels were not measured during the study but potential signs and symptoms of copper overload including neuropsychiatric and hepatotoxicity events were reported as AEs.
  - FDA grouped term: SOC Nervous system disorders
    - Nervous system disorders were reported in 5% vs 8.3% of participants in Arm A and Arm B, respectively.
      - The most common AEs in Arm A were headaches (2.5%) and seizures (1.4%).
      - The most common AEs in Arm B were seizures (3%) and headaches (2.8%).
  - FDA grouped term: SOC Psychiatric disorders
    - Psychiatric disorders were reported in 0.6% and 0.8% of participants in Arm A and Arm B, respectively.
  - Hepatotoxicity:
    - ALT increases (all grade and Grade ≥ 3) occurred more often in Arm B (see Table 10). The incidence of AST increases was similar between arms.
    - FDA review of potential liver manifestations of copper overload included abdominal pain, ascites, upper GI bleeding, and liver failure/dysfunction: Although these AEs may represent nonspecific findings, in this study such events were reported in 0.2% of participants in Arm A and 2.8% in Arm B. The participant in Arm A had ascites in the setting of infectious enterocolitis. The most commonly reported event in Arm B was abdominal pain (1.4%). All events occurred in Induction 1 and were Grade 3 with the exception of one participant in Arm B without documented liver involvement at baseline who had an event of Grade 5 hepatic failure on Day 15. Minimal details were available in the narrative.

Reviewer Comment: Nervous system disorders including seizures, ALT increases, and potential signs/symptoms of liver failure were reported at a numerically higher incidence in

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participants treated with CPX-351 compared to those treated with DA, though none occurred with a difference of ≥ 5% between arms except for ALT increases. There is insufficient information in the submission to determine whether any of the AEs reported in Arm B were directly related to copper overload.

Laboratory AEs

Minimal laboratory data were available in this submission. As noted in the CSR, routine laboratory monitoring was conducted but were not collected and "Adverse events identified from laboratory parameters as defined in the protocol were reported on the AE CRF." The most common laboratory abnormalities reported by PT are included in Table 10 above.

The Applicant provided an analysis of time to count recovery by treatment cycle. Time to neutrophil and platelet recovery were substantially longer in Arm B during both induction cycles, with the greatest difference in Induction 2. This delay in count recovery corresponded to longer hospitalization for participants in Arm B, especially in Induction 2 where the median duration of hospitalization was 34 days (range 1, 97) for Arm B compared to 25 days (range 7, 41) for Arm A. During these cycles, sepsis and bleeding events were more common in Arm B.

Table 11. AAML1831 – Time to Count Recovery

	Arm A (DA-GO) N = 361	**Arm B (CPX-351-GO) N = 357**
Induction 1		
• Time to ANC recovery to >0.5 Gi/L, median (range)	31 days (12, 62)	34 days (12, 67)
• Time to platelet recovery to >50 Gi/L, median (range)	29 days (14, 45)	33 days (11, 56)
Induction 2		
• Time to ANC recovery to >0.5 Gi/L, median (range)	29 days (10, 44)	40 days (11, 105)
• Time to platelet recovery to >50 Gi/L, median (range)	23.5 days (11, 44)	34 days (11, 69)

Source: Excerpted from AAML1831 CSR Table 11

Reviewer Comment: Based on the adult data supporting the original approval[5], the median time to neutrophil recovery in Induction 2 was 35 days (range: 5, 78) for those who received CPX-351. However, during the two cycles of induction no difference in infection between the CPX-351 and 7+3 arms was noted. In AAML1831, the median time to neutrophil recovery for the CPX-351 arm was 40 days (range: 11, 105) in Induction 2. In contrast to the adult data, the delayed count recovery was associated with a significantly increased incidence of infection in the CPX-351 arm compared to the DA arm. These observations may be due, at least in part, to the use of a higher dose of CPX-351 in AAML1831 than the approved dose causing prolonged profound myelosuppression.

[5] NDA Multidisciplinary Review and Evaluation for NDA 209401 dated 8/3/17

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8.3.3 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Infusion-related reactions (IRR) have been reported in patients who received CPX-351 in the postmarket setting. In AAML1831, IRR was reported at a similar rate in the CPX-351 arm compared to DA (0.5% in each arm).

8.3.4 Integrated Assessment of Safety

The safety findings from AAML1831 were consistent with known safety profile of CPX-351 from the randomized trial in adults with newly diagnosed t-AML or AML-MRC which supported the original NDA approval. In Induction Cycle 1 and 2,

- The median times to count recovery for both neutrophils and platelets were longer in the CPX-351 arm. This corresponded to an increase in the incidence of infections and bleeding events was observed in the CPX-351 arm compared to the DA arm, and the duration of hospitalization was longer in the CPX-351 arm during Induction 2.
- The incidences of all grade and Grade ≥ 3 hypertension, rash, and infections were substantially higher (> 10% risk difference) in the CPX-351 arm compared to the DA arm.
- Rash accounted for the majority of hypersensitivity events that occurred on study.
- The incidence of SOC Cardiac disorders was numerically higher in the CPX-351 arm, but the overall incidence was low.
- Nervous system disorders including seizures, ALT increases, and potential signs/symptoms of liver failure were reported at a numerically higher incidence in participants treated with CPX-351, though none occurred with a difference of ≥ 5% between arms except for ALT increases. Copper levels were not measured, and there is insufficient information in the submission to determine whether any of the AEs reported in Arm B were directly related to copper overload which is a known risk of CPX-351.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

The EFS event dates for induction failure and relapse were recorded as "reporting period end dates" rather than actual event dates. Specifically, induction failure was dated as the last day of the treatment cycle in which failure occurred, while relapse dates were inconsistently recorded—using actual dates when available but defaulting to the last day of the treatment cycle when actual dates were unavailable. This approach introduces interval censoring and the potential for differential measurement error, which could yield biased survival estimates and invalid statistical inference. The use of proxy dates violates fundamental assumptions of the

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standard Kaplan-Meier and Cox proportional hazards methods, which assume precisely observed event times. Consequently, the statistical validity of the primary efficacy analysis may be compromised.

EFS was numerically worse in the experimental arm. The prespecified statistical analysis plan did not include a boundary for harm. Such a boundary is uncommon in oncology and would typically be used only in scenarios in which the hypothesis of interest is truly two-sided (e.g. trials comparing two therapies approved and commonly used in a disease area which are intended to inform practice of medicine). Absence of a boundary for harm as well as reproducible data to support EFS preclude a formal conclusion of inferior EFS for the experimental arm.

8.5 Conclusions and Recommendations

The results of AAML1831 were not sufficient to establish the efficacy or safety of CPX-351 for the treated population with newly diagnosed de novo AML. The study was stopped for futility at a preplanned interim analysis based on a reported EFS HR of 1.39 (95% CI: 1.09-1.77) and an OS HR of 1.08 (95% CI: 0.78-1.48). In the analysis of EFS, induction failures, relapses, and deaths were all more common in the CPX-351 arm compared to the DA arm. The Applicant's analysis of safety and FDA's additional analyses were consistent with known safety profile of CPX-351 from the randomized trial in adults with newly diagnosed t-AML or AML-MRC. Hypertension, rash, and infections were substantially higher (>10% risk difference) in the CPX-351 arm. The median times to count recovery for both neutrophils and platelets were also longer in the CPX-351 arm.

The review team recommends approval of the supplement with revisions to Section 8.4 of the USPI to state that the safety and effectiveness of CPX-351 for treatment of newly diagnosed de novo AML have not been established.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

There was no advisory committee meeting or external consultation for this NDA supplement.

10 PEDIATRICS

On August 28, 2020, the Agency issued a pediatric Written Request (PWR) for studies to provide data to determine a safe and appropriate pediatric dose and to determine the efficacy of CPX-

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351 as a component of a multidrug regimen for de novo AML. Studies in neonates and infants less than 1 year were requested in the newly-diagnosed de novo AML setting. The PWR included three pediatric clinical studies. Data from Study 1 (AAML1421) and Study 2 (CPX-MA-1201) were included in S-006, which extended the intended population to patients 1 year and older for the original indication for t-AML and AML-MRC. Data from Study 3 (AAML1831) for de novo AML were included in the current supplement. Although Study 3 was not a positive study and did not support a new indication, the Division concluded that the terms of the PWR were met. The details of the Division's evaluation of the Applicant's response to the PWR is provided in a separate review.[1]

This submission was discussed by OCE-PeRC on 11/12/2025 and by the Pediatric Exclusivity Board on 12/3/2025. The Pediatric Exclusivity Board voted to grant pediatric exclusivity.

11 LABELING RECOMMENDATIONS

11.1 Prescribing Information

The table below summarizes major changes to the prescribing information made by FDA. See the final approved prescribing information for Vyxeos accompanying the approval letter for more information.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
8.4 Pediatric Use	The Applicant proposed language to update subsection 8.4 based on findings from an open-label, randomized study (NCT04293562), including a statement that “no new safety signals were identified” in the Vyxeos arm and “The safety and effectiveness of VYXEOS in pediatric patients with de novo AML has not been established.”	FDA made changes throughout subsection 8.4 to align with FDA guidance and best labeling practices, including adding a concise description of the AAML1831 trial and including the number and age range of pediatric patients included in the Vyxeos arm. FDA also added a statement about exposures of total daunorubicin and cytarabine observed in pediatric patients compared to adults given the same dose based on body surface area.

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11.2 Patient Labeling

There is no patient labeling associated with this product.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

12.1 Recommendations on REMS

No new safety issues have been identified that would warrant consideration of a REMS.

13 POSTMARKETING REQUIREMENTS AND COMMITMENTS

None.

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14 APPENDICES

14.1 References

None

14.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): AAML1831

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 3,160		
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):		
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)): 66, data on categories not collected 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 X
Is a description of the steps taken to minimize potential bias provided:	Yes X CSR 3.4.2	No
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3,094		
Is an attachment provided with the reason:	Yes	No X This large, randomized study with negative results does not demonstrate the efficacy of CPX-351 to support a new indication. The 2% of investigators with potential financial interests are unlikely to alter this conclusion.

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14.3 Nonclinical Pharmacology/Toxicology

None.

14.4 OCP Appendices

None

14.5 Additional Clinical Analyses

None.

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15 DIVISION DIRECTOR (DHM1)

x
Director, Division of Hematologic Malignancies 1 (DHM1)

Reference ID: 5734496

NDA Multidisciplinary Review and Evaluation
NDA 209401 S-018
Vyxeos® (daunorubicin and cytarabine) liposome

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Ritu Chadda, PhD	OCP/DCPI	Sections: 6	X Authored Approved
	Signature: Ritu Chadda -S Digitally signed by Ritu Chadda -S Date: 2025.12.31 12:36:38 -05'00'			
Clinical Pharmacology Team Leader	Hongfei Zhang, PhD	OCP/DCPI	Sections: 6	Authored X Approved
	Signature: HONGFEI ZHANG -S Digitally signed by HONGFEI ZHANG -S Date: 2025.12.31 10:26:00 -05'00'			
Statistical Reviewer	Huijun Jiang, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
	Signature: HUIJUN JIANG -S Digitally signed by HUIJUN JIANG -S Date: 2025.12.31 11:27:57 -05'00'			
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: JONATHON J. VALLEJO -S Digitally signed by JONATHON J. VALLEJO -S Date: 2026.01.09 23:06:32 -05'00'			
Division Director (Statistical)	Yuan Li Shen, DrPH	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: YUAN-LI SHEN -S Digitally signed by YUAN-LI SHEN -S Date: 2026.01.15 09:44:05 -05'00'			
Clinical Reviewer	Emily Jen, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	X Authored Approved
	Signature: EMILY Y. JEN -S Digitally signed by EMILY Y. JEN -S Date: 2026.01.03 18:46:22 -05'00'			
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	Authored X Approved
	Signature: Donna Przepiorka -S 2025.12.31 09:41:23 -05'00'			

NDA Multidisciplinary Review and Evaluation
NDA 209401 S-018
Vyxeos® (daunorubicin and cytarabine) liposome

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Associate Director for Labeling	Evan Bryson, PharmD, BCOP	OOD	Sections: 11	X Authored Approved
	Signature: Evan B. Bryson -S Digitally signed by Evan B. Bryson -S Date: 2026.01.08 12:52:14 -05'00'			
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 5, 12, 13	X Authored Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	Kelly Norsworthy, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
01/27/2026 08:20:11 AM

KELLY J NORSWORTHY
01/27/2026 09:06:40 AM