NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 209401 S-006**
Application Type	SE5
Priority or Standard	Priority
Submit Date	10/7/2020
Received Date	10/7/2020
PDUFA Goal Date	4/7/2021
Office/Division	OOD/DHM1
Review Completion Date	3/30/2021
Applicant	Jazz Pharmaceuticals
Established/Proper Name	(Daunorubicin and cytarabine) liposome injection
(Proposed) 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]
Applicant Proposed Indication/Population	For the treatment of adults and pediatric patients aged 1 year and older with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	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.
SNOMED CT for the Recommended Indication/Population	91861009, 721306009, 445448008
Recommended 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

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.

Table of Contents

Table of Tables

Table of Figures

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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

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		

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 is approved for treatment of adults with newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). A Written Request was issued to investigate the potential use of Vyxeos in the treatment of acute myeloid leukemia in pediatric patients 1 to < 17 years old. Supplement 006 contains the results of Study 1 and Study 2 of the Written Request, and the Applicant proposed to use these data to expand the approved indication to pediatric patients ages 1 year and older with (b) (4) dosing regimen.

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 "for 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" 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 with extrapolation of the efficacy to the pediatric population.

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/m2 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.

Study 301 enrolled 309 patients, with 153 randomized to Vyxeos and 156 randomized to the 7+3 control arm. The primary endpoint of Study 301 was 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 log- rank p-value of 0.005, indicating a survival benefit with Vyxeos treatment. The HRs for OS were consistent on subgroup analysis by disease subtype.

This supplement did not include any efficacy studies of Vyxeos as first line therapy for children with t-AML or AML-MRC. Pharmacokinetics (PK), activity and safety data were provided from two pediatric clinical trials. CPX-MA-1201 was a single-arm dose-escalation trial of Vyxeos (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome or (daunorubicin 59.4 mg/m^2 and cytarabine 135 mg/m^2) liposome in 27 patients 1 - 21 years old with relapsed or refractory (R/R) AML or ALL. AAML1421 was a single arm trial of Vyxeos (daunorubicin 59 mg/m^2 and cytarabine 134 mg/m^2) liposome in 38 patients 1 - 21 years old with R/R AML.

PK data were available for a total of 46 children. The population PK models based on data from pediatric and adult patients treated with Vyxeos indicated that the exposures of total daunorubicin and cytarabine observed in pediatric patients were consistent with the values observed in adults given the same dose based on BSA. In exposure-response analyses, cytarabine exposure was a significant covariate for clinical activity (complete remission) and safety (neutropenia and rash) outcomes, but age was not significant, supporting the appropriateness of exposure-matching.

The etiopathogeneses and natural histories of t-AML and of AML-MRC are essentially the same in adult and pediatric patients. Additionally, the approach to standard-of-care therapy for AML (intensive cytotoxic regimens based on daunorubicin and cytarabine) is also the same for adult

and pediatric patients with AML, since there is no known difference in sensitivity of the AML cells to chemotherapy based on age rather than mutation profile. Lastly, the population PK models confirmed that the recommended dose provided appropriate exposure. These data provide substantial evidence to support extrapolation of efficacy from the adult indication to the pediatric population 1 year and older.

1.3 Benefit-Risk Assessment

	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 rare in children • The diagnostic criteria for t-AML and AML-MRC are the same in adults and children. • The approach to treatment of t-AML and AML-MRC is the same for adults and children. • The molecular pathogenesis of t-AML and AML-MRC is the same for adults and children.	• t-AML and AML-MRC are fatal diseases. • t-AML and AML-MRC have the same biology in adults as in pediatric patients.
Current Treatment Options	• Daunorubicin/cytarabine-based regimens are standard treatment of AML • Long-term survival of patients with t-AML or AML-MRC is poor.	• There is a need for an effective agent for treatment of t-AML and AML-MRC in children.
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). • In population PK models and exposure-response analyses, the current recommended dose was adequate for matching exposure in children to that in adults.	• There is substantial evidence in adults of effectiveness for Vyxeos as treatment for t-AML and AML-MRC. • Based on the biological similarity and exposure-matching, efficacy can be extrapolated to children.
Risks and Risk Management	• The safety profile in children is similar to that established in adults.	• No additional risk management is needed for use of Vyxeos in children.

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. Based on diagnostic criteria, molecular studies and standard-of-care approach to treatment, t-AML and AML-MRC are similar in children and adults. The original approval of Vyxeos was based on the results of Study 301, showing a survival benefit for adults with t-AML and AML-MRC in comparison to standard 7+3. PK studies and exposure-response analyses support extrapolation of efficacy from the adult indication to children.

The safety profile of Vyxeos was established with the original approval. Safety data were available from 46 children 1 - < 17 years old treated with Vyxeos in two single-arm trials. No new safety signals were observed in pediatric patients in these two single-arm trials. No differences in safety were observed by age. In the assessment of safety across doses, there were increased risks for cardiac toxicity and high-grade infections with doses of Vyxeos higher than that recommended. (b) (4)

The safety data support Vyxeos (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) as the pediatric dose for the proposed indication.

Based on extrapolation of efficacy and the observed safety profile, it is reasonable to conclude that the benefit-risk assessment favors approval of Vyxeos for treatment of children 1 year and older with t-AML or AML-MRC.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

□	The patient experience data that was submitted as part of the application, include:	Section
	□ Clinical outcome assessment (COA) data, such as	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	
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 the second most common form of leukemia in children. In the United States, approximately 800 patients per year under the age of 20 are diagnosed with AML (American Cancer Society, 2020). The 5-year survival rate is 66% (Gibson, 2005; Siegel, 2020).

Therapy-related AML (t-AML)

The WHO 2016 classification of therapy-related myeloid neoplasms (t-MN) includes t-AML, which is defined as AML occurring as a late complication of cytotoxic chemotherapy and/or radiation. The definition establishes the diagnosis irrespective of the patient's age. In SEER, t-AML accounted for less than 10% of the cases of AML, and among patients with t-AML, 2% were less than 20 years old (Dores et al. 2012).

t-AML is thought to arise from pre-existing clones with mutations in DNA damage repair genes that are subsequently selected as resistant to the prior chemotherapy or radiation and with acquisition of additional driver mutations (Ganser et al. 2017). In contradiction to this, a recent study concluded that, in comparison to t-MN in adults, t-MN in children arose solely by treatment-induced acquisition of mutations rather than selection of pre-existing clones (Schwartz et al. 2021). However, more recent evidence suggests that pre-existing clonal mutations at ultra low frequencies can be tracked back to very early in life, taking up to 30 years to reach 1% frequency and be detectable (Williams N et al. 2020). Thus, the current disease model allows for a uniform pathogenesis across age groups (Bolton et al. 2020).

Children with t-AML have a worse prognosis compared to those with de novo AML, with 5-year survival rates of 6–11% if not treated with hematopoietic stem cell transplantation (HSCT) (Brown, 2018; Tsurusawa, 2005).

AML with Myelodysplasia-Related Changes (AML-MRC)

The WHO 2016 classification defines AML-MRC as AML that has evolved from prior MDS or MDS/MPN, that has established MDS-related cytogenetic abnormalities (with the exception of del(9q)), or that has dysplasia in ≥ 50% of cells in 2 or more myeloid lineages (the latter in the absence of favorable NPM1 or biallelic CEBPA mutations). The definition establishes the diagnosis irrespective of the patient's age. A majority of both adult and pediatric patients with AML-MRC fall under the latter two criteria, and the most commonly occurring MDS-related cytogenetic abnormalities are comparable in the two populations (-7, del(7q), del(5q), and complex karyotype).

In SEER, AML-MRC accounted for 24-35% of the cases of AML (Koenig, 2020), but it is rare in children. In SEER-17, among patients with AML-MRC, fewer than 10% were less than 20 years old (Dores et al. 2012). Among pediatric patients with AML, about 20% have AML-MRC, with the incidence being highest in those under 2 years of age (38%) (Kinoshita, 2014; Koenig, 2020).

Outcomes in patients with AML-MRC tend to be worse than in those without AML-MRC, with 3-year survival rates around 57% for pediatric patients and median overall survival of 9 to 12 months for adult patients (Kinoshita, 2014; Koenig, 2020).

2.2 Analysis of Current Treatment Options

The approach to therapy is similar for patients with t-AML , AML-MRC, or de novo AML. There are no data to suggest that sensitivity of AML cells to cytotoxics or targeted therapies varies by age of patient once the mutation profile is taken into account. The standard-of-care for first-line treatment of patients with AML with curative intent includes intensive combination induction, consolidation and/or allogeneic HSCT (NCCN Guidelines, 2021). Additional targeted agents may be used depending on the mutational profile and genetic risk irrespective of the subtype (NCCN Guidelines, 2021).

Table 1 shows the approved therapies for first-line treatment of 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 ozagamicin. The latter is generally not used for treatment of patients with t-AML or AML-MRC, since the addition of gemtuzumab had no clinical benefit with adverse cytogenetics, which are prevalent in patients with t-AML or AML-MRC. The only therapy approved specifically for the treatment of t-AML or AML-MRC is Vyxeos (CPX-351), and that approval is limited to adults.

Table 1. Available Therapy for 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
Enasidenib	For treatment of adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test.
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.

Table 1. Available Therapy for Treatment of AML

Agent	Excerpted Indication
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
Gilteritinib	For the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.
Idarubicin	In combination with other approved anti-leukemic drugs for treatment of AML in adults
Ivosidenib	For treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test; and 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 adult patients who are ≥ 75 years old 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
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 treatment of adults with a diagnosis of therapy-related AML or AML with myelodysplasia-related changes

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.

The relied-upon listed drugs DepoCyt (cytarabine; NDA 021041) and DaunoXome (daunorubicin citrate; NDA 050704) have been discontinued. Neither listed drug was discontinued for reasons of safety/effectiveness.

3.2 Summary of Presubmission/Submission Regulatory Activity

Presubmission interactions with the Applicant were conducted under IND 072939.

- December 3, 2019 – Type B meeting with Sponsor to discuss plan for submission of sNDA (b) (4) data from CPX-MA-1201 and Study 205. The Agency noted that the data from the listed studies (b) (4) that PK and safety data from the pediatric studies might support a labeling update of Section 8.4.

- August 28, 2020 – FDA issued Written Request to obtain data to support efficacy and safety of Vyxeos in the pediatric population (WR includes 3 studies: AAML1421, CPX-MA-1201, (b) (4)

- 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 WR)

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

4.1 Office of Scientific Investigations (OSI)

This supplement does not support an efficacy claim based on new efficacy data. Since there were no new efficacy endpoint data to be confirmed, no clinical site inspections were requested.

4.2. Product Quality

There was no new product quality information submitted in this supplement. The Applicant claimed a categorical exclusion from the requirements to prepare an environmental assessment or an environmental impact statement in accordance with 21 CFR 25.31(b), and the Product Quality Review team recommended that the categorical exclusion be granted.

4.3 Devices and Companion Diagnostic Issues

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

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There were no new nonclinical data submitted in this supplement.

6 CLINICAL PHARMACOLOGY

6.1 Executive Summary

VYXEOS (CPX-351) received FDA approval on Aug. 3, 2017, for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). The current supplement (NDA 209401/S-006) proposes to expand the currently approved indication to include pediatric patients aged 1 year and older. The Applicant proposes to extrapolate efficacy from the adult data submitted in the original NDA with safety and pharmacokinetic data from two independently conducted studies of CPX-351 in pediatric and young adult patients with relapsed or refractory (R/R) AML.

- Study CPX-MA-1201: Phase 1, open-label, dose escalation study of CPX-351 in 27 pediatric and young adult patients (age range 1 to 19 years) with R/R hematologic malignancies.
- Study AAML1421: Phase 1/2, open-label, dose escalation study of CPX-351 followed by fludarabine, cytarabine, and filgrastim (FLAG) in 38 pediatric and young adult patients (age range 1 to 21 years) with R/R AML.

The key review questions focus on appropriate dose selection in pediatric patients with newly-diagnosed t-AML or AML-MRC based on an exposure-matching approach. The pharmacokinetics of daunorubicin and cytarabine after administration of CPX-351 were evaluated in pediatric patients aged 1 year and older in Studies CPX-MA-1201 and AAML1421.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209401/S-006. This sNDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	Evidence of effectiveness in pediatric patients aged 1 year and older with newly-diagnosed t-AML or AML-MRC is extrapolated from previously completed studies in adult patients.

Review Issue	Recommendations and Comments
General dosing instructions	The recommended dosing regimen of CPX-351 for pediatric patients aged 1 year and older with newly-diagnosed t-AML or AML-MRC is as follows: • First Induction: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1, 3, and 5 • Second Induction (only for patients failing to achieve a response with the first induction cycle): (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1 and 3 • Consolidation: (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome IV on Days 1 and 3 The recommended dosing regimen in pediatric patients is identical to the previously approved regimen in adults.
Dosing in patient subgroups	No clinically meaningful effects on the pharmacokinetics of daunorubicin and cytarabine were observed based on age (1 to 81 years), sex, race (White, Black, Asian), body weight (9 to 156 kg), body mass index (14 to 48 kg/m^2), and white blood cell count (0.2 to 111 Gi/L) after adjusting dose by body surface area.
Labeling	The proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Pharmacology and Clinical Pharmacokinetics of CPX-351 were reviewer previously. Refer to the original multidisciplinary review for NDA 209401. New or updated information based on the current supplement is summarized below.

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.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen of CPX-351 for adults and pediatric patients aged 1 year and older with newly-diagnosed t-AML or AML-MRC is as follows:

- First Induction: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1, 3, and 5
- Second Induction (only for patients failing to achieve a response with the first induction cycle): (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1 and 3
- Consolidation: (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome IV on Days 1 and 3

Therapeutic Individualization

No clinically meaningful effects on the pharmacokinetics of daunorubicin and cytarabine were observed based on age (1 to 81 years), sex, race (White, Black, and Asian), body weight (9 to 156 kg), body mass index (14 to 48 kg/m^2), and white blood cell count (0.2 to 111 Gi/L) after adjusting dose by body surface area.

Outstanding Issues

At the time of initial approval, PMR 3255-2 was issued to complete a clinical PK trial to determine an appropriate dose of CPX-351 to minimize toxicity in patients with moderate and severe renal impairment. This PMR has not yet been fulfilled. Refer to the original multidisciplinary review for NDA 209401 for additional details. No new Clinical Pharmacology PMRs will be issued for the current sNDA.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The General Pharmacology and Pharmacokinetic Characteristics of CPX-351 were reviewed previously. Refer to the original multidisciplinary review for NDA 209401.

Age (1 to 81 years) was not a significant covariate for exposure of daunorubicin or cytarabine after adjusting for body surface area (BSA). Median exposure in pediatric patients was slightly higher compared to adults; however, the exposures of total daunorubicin and cytarabine observed in pediatric patients were within the values observed in adults given the same dose based on BSA. The differences in exposure are not anticipated to be clinically meaningful.

In Studies CPX-MA-1201 and AAML1421, total daunorubicin and its active metabolite daunorubicinol, as well as total cytarabine and its inactive metabolite 1-β-D-arabinofuranosyluracil (Ara-U) were measured using validated LC/MS/MS methods. During the studies, the original analytical site used for prior studies in adults and early samples from the two pediatric studies closed and the methods were transferred to a new analytical site. The new analytical site performed a bridging study by reanalyzing a subset of samples previously analyzed at the original analytical site and comparing the results. The bridging results were deemed acceptable (at least 67% of samples within ±20%). As a result, a portion of samples from the two pediatric studies were analyzed and reported from the new analytical site.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The effectiveness of CPX-351 in pediatric patients aged 1 year and older with newly-diagnosed t-AML or AML-MRC is extrapolated from evidence of effectiveness in adults. Refer to the original multidisciplinary review for NDA 209401 for detailed review of CPX-351 effectiveness in adults with newly-diagnosed t-AML or AML-MRC. In adults with newly-diagnosed t-AML or AML-MRC, treatment with the approved recommended regimen of CPX-351 resulted in improved overall survival compared to conventional 7+3 (cytarabine + daunorubicin) chemotherapy. Median (95% CI) overall survival was 9.6 (6.6, 11.9) months in the CPX-351 arm and 5.9 (5.0, 7.8) months in the 7+3 arm.

The safety and PK of CPX-351 were evaluated in two studies of CPX-351 in pediatric and young adult patients with relapsed or refractory (R/R) AML.

- Study CPX-MA-1201: Phase 1, open-label, dose escalation and expansion study of CPX-351 in 27 pediatric and young adult patients (age range 1 to 19 years; median 5 years) with R/R AML or acute lymphocytic leukemia (ALL). Two dose levels of CPX-351 were evaluated: daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 on Days 1, 3, and 5 (n=22) and daunorubicin 59 mg/m^2 and cytarabine 134 mg/m^2 on Days 1, 3, and 5 (n=5). Two patients at the higher dose level experienced DLTs (Grade 3 headache in a 2-year-old patient and Grade 3 pain in a 16-year-old patient); therefore, the maximum tolerated dose was daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 on Days 1, 3, and 5.

- Study AAML1421: Phase 1/2, open-label, dose-escalation and expansion study of CPX-351 followed by fludarabine, cytarabine, and filgrastim (FLAG) in 38 pediatric and young adult patients (age range 1 to 21 years; median 11 years) with R/R AML. One dose level of CPX-351 was evaluated: daunorubicin 59 mg/m^2 and cytarabine 135 mg/m^2 on Days 1, 3, and 5. One DLT was observed in the first six patients (Grade 3 decreased ejection fraction); therefore, daunorubicin 59 mg/m^2 and cytarabine 135 mg/m^2 on Days 1, 3, and 5 was deemed the recommended Phase 2 dose and additional patients were enrolled.

No new safety signals were observed in pediatric patients in these two single-arm trials. No differences in safety were observed by age. Refer to **Section 8.3** for detailed review of safety in these two studies.

The Applicant provided population PK models to identify a dosing regimen in pediatric patients expected to match adult exposure and exposure-response analyses for safety and efficacy to support similarity of concentration-response relationships in adult and pediatric patients. These analyses are described in detail in **Section 6.3.2.2**.

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

The approved recommended dosing regimen of CPX-351 for adult patients with newly-diagnosed t-AML or AML-MRC is as follows:

- First Induction: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1, 3, and 5
- Second Induction (only for patients failing to achieve a response with the first induction cycle): (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1 and 3
- Consolidation: (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome IV on Days 1 and 3

The Applicant's proposed dosing regimen of CPX-351 for pediatric patients aged 1 year or older with newly-diagnosed t-AML or AML-MRC was (b) (4) .

(b) (4) For the pediatric full extrapolation approach, the efficacy of CPX-351 in pediatric patients with newly-diagnosed t-AML or AML-MRC is extrapolated from results in adult patients with newly-diagnosed t-AML or AML-MRC and the pediatric dosing regimen is determined based on exposure-matching to the approved adult dosing regimen.

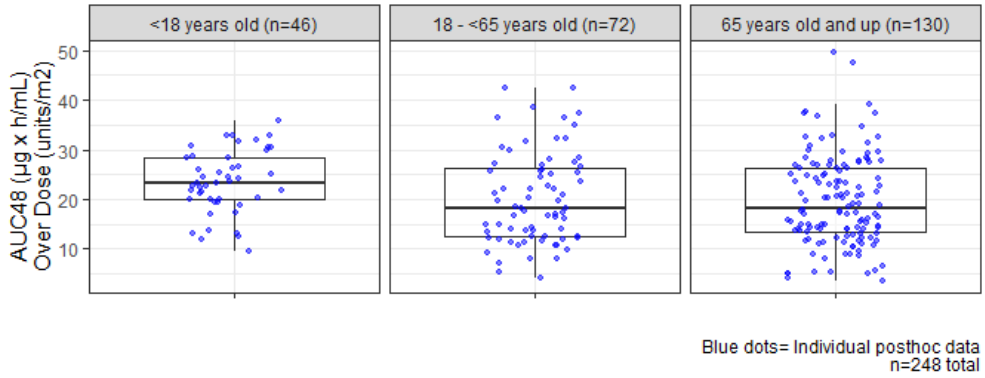
Population PK Models: To evaluate the exposure-matching approach and the adequacy of the adult regimen in pediatric patients, PK data from pediatric and young adult patients with R/R AML were collected in Studies CPX-MA-1201 and AAML1421 to characterize the PK of daunorubicin and cytarabine in pediatric patients. These data were added to previously-developed population PK models (separate models for total daunorubicin and total cytarabine) built using data from adult patients with hematologic malignancies. Refer to **Section 15.4** for detailed review of the updated population PK models and the original multidisciplinary review for NDA 209401 for review of the original population PK models.

The population PK models included data from 250 patients including 46 pediatric patients (n=22 aged 1 to <6 years, n=10 aged 6 to <12 years, and n=12 aged 12 to <18 years) treated with CPX-351. For both daunorubicin and cytarabine, body surface area (BSA) was a significant covariate on the central volume of distribution (Vc) and clearance. Given the effects of BSA on exposure, CPX-351 is dosed using a BSA-based regimen (i.e., mg/m^2). After accounting for BSA, age was

not a significant covariate when modeled as either a continuous or categorial covariate. Disease state (R/R AML, newly-diagnosed AML, MDS, or R/R ALL) was not a significant covariate.

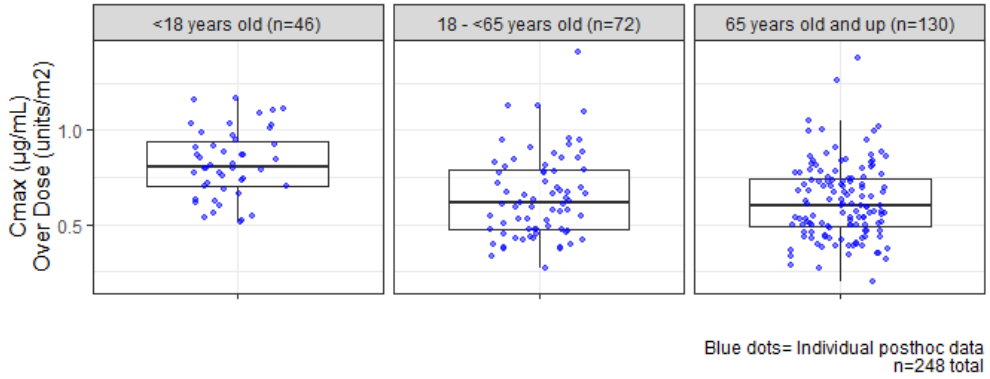
Using the updated population PK models, estimates of daunorubicin and cytarabine exposure were compared across age groups. While the median exposure in pediatric patients was slightly higher compared to adults, the exposures of total daunorubicin and cytarabine observed in pediatric patients were within the values observed in adults given the same dose based on body surface area (**Figure 1** and
Figure 2). The slight differences in the exposure are not anticipated to be clinically meaningful.

Figure 1: Estimates of Total Cytarabine $AUC_{0\text{-}48h}$ by Age



Source: Reviewer's Analysis, Appendix 15.4

Figure 2: Estimates of Total Cytarabine C_{max} by Age



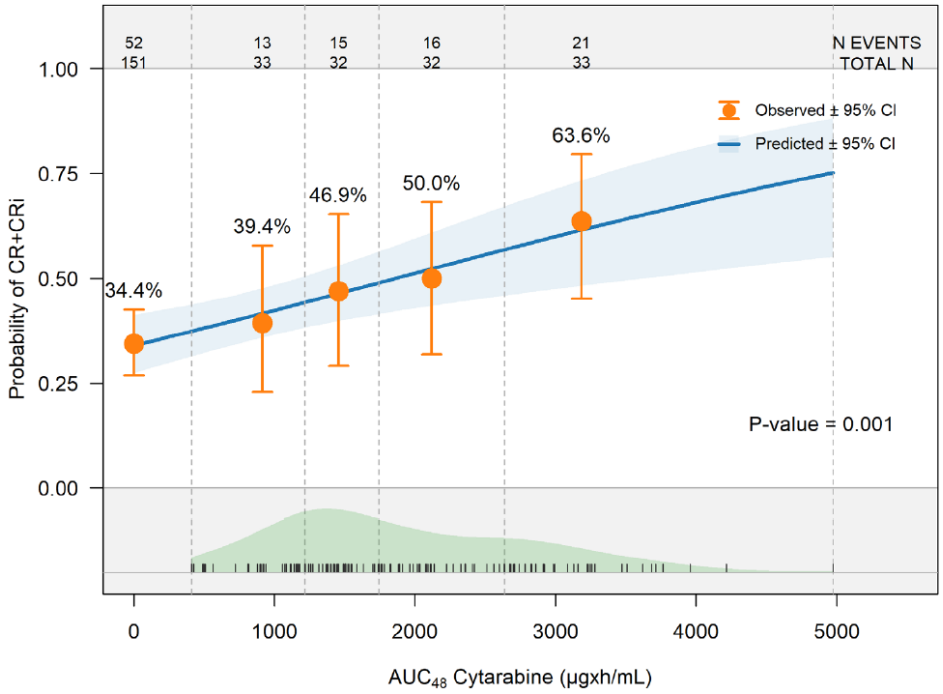
Source: Reviewer's Analysis, Appendix 15.4

Exposure-Response Analyses for Efficacy: Two separate exposure-response analyses for efficacy were conducted:

1. [redacted] (b) (4)
2. Adult patients with newly-diagnosed t-AML or AML-MRC (Study CLTR0310-301)

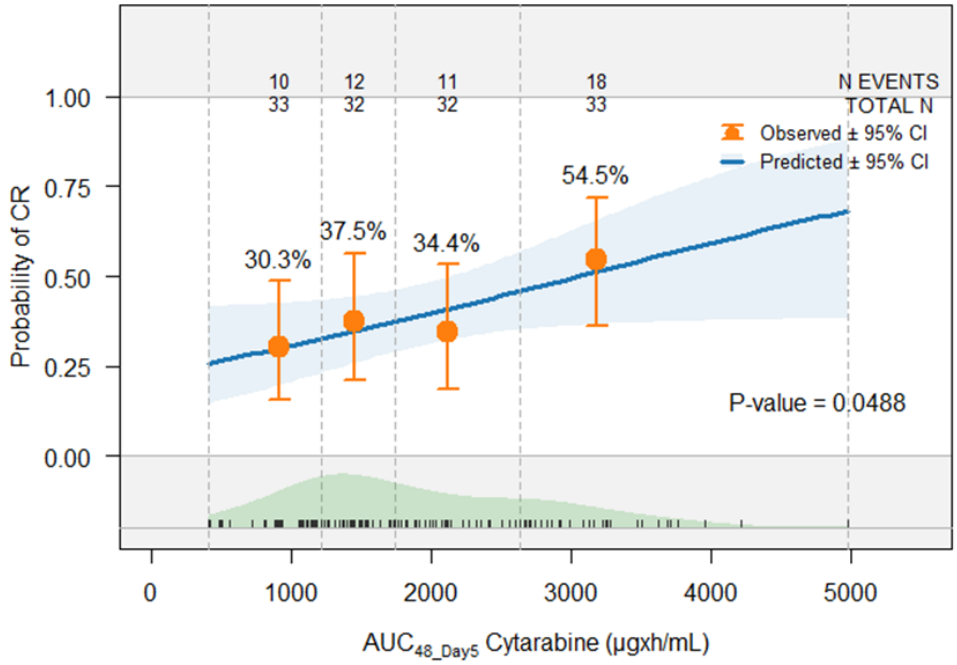
The E-R analysis for efficacy in adults with newly-diagnosed t-AML or AML-MRC included 130 patients treated with CPX-351 at a dose of 44:100 mg/m^2 and 151 patients treated with conventional daunorubicin and cytarabine (7+3). In the Applicant's analysis, cytarabine $AUC_{0\text{-}48h}$ was fixed at 0 for all patients in the conventional 7+3 arm. Cytarabine exposure ($AUC_{0\text{-}48h}$) was a statistically significant covariate for probability of CR or CRi (**Figure 4**) and for CR alone. FDA modified the Applicant's analysis to include only patients treated with CPX-351. Among patients treated with CPX-351, cytarabine exposure ($AUC_{0\text{-}48h}$) was a statistically significant covariate for probability of CR (**Figure 5**).

Figure 4: Probability of CR or CRi as a Function of Cytarabine AUC0-48h in Adults with Newly-Diagnosed t-AML or AML-MRC



Source: Report JAZP-PMX-CPX351-2171_SIM, Figure 3

Figure 5: Probability of CR as a Function of Cytarabine AUC0-48h in Adults with Newly-Diagnosed t-AML or AML-MRC



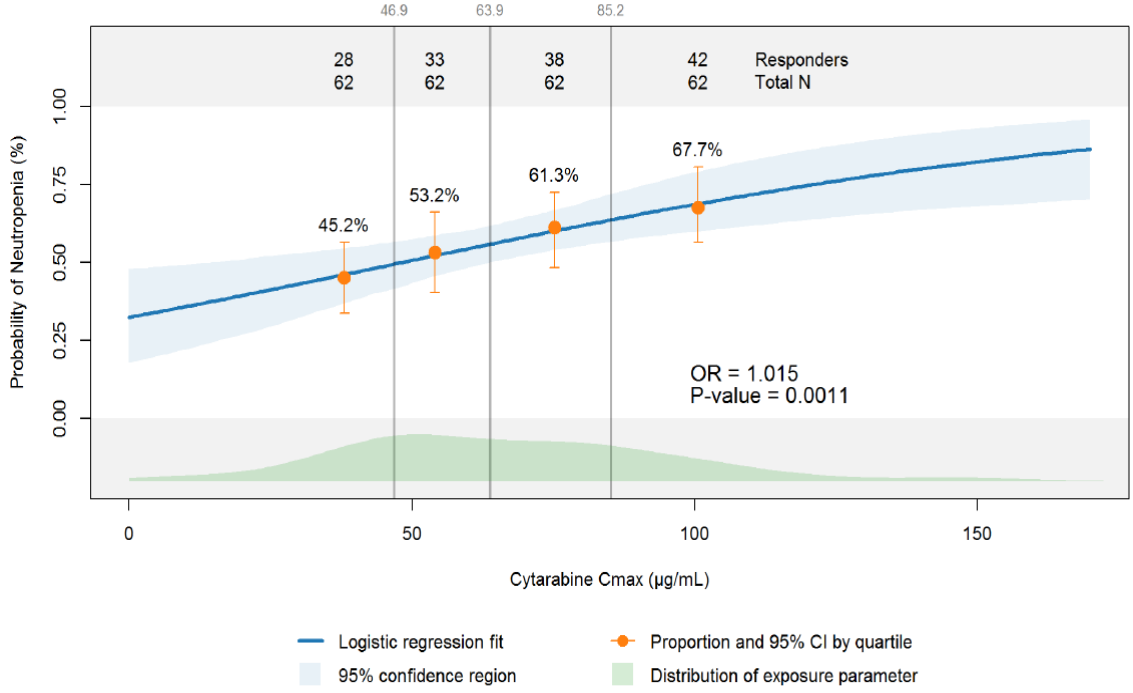
Source: Reviewer's Analysis, Appendix 15.4

Together, the two exposure-response analyses support a similar exposure-response relationship for CPX-351 efficacy in both pediatric and adult patients.

Exposure-Response Analyses for Safety: The Applicant pooled patients from all age groups and studies (Studies CPX-MA-1201, AAML1421, CLTR0305-101, CLTR0310-206, and CLTR0310-301) to conduct exposure-response analyses for safety. Safety endpoints evaluated were probability of neutropenia, probability of rash, time to neutrophil recovery, time to platelet recovery, and probability of all Grade and Grade 3-5 treatment-emergent adverse events (TEAEs).

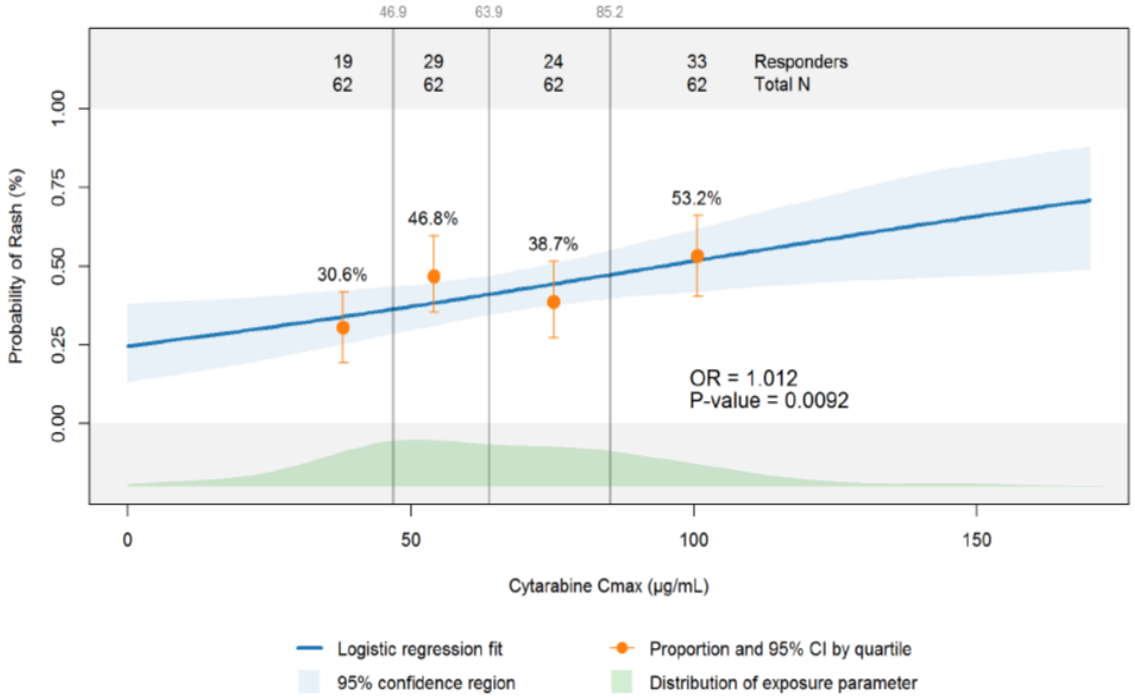
The exposure-response analyses identified a positive relationship between drug exposure and probability of neutropenia and rash (**Figure 6** and **Figure 7**). Age was not a significant covariate when modeled as either a continuous or categorical covariate. Of note, safety events (including neutropenia) were based on reported AEs in all studies rather than laboratory values. Based on these results, exposure-response relationships for CPX-351 safety appear similar in both pediatric and adult patients.

Figure 6: Probability of Neutropenia as a Function of Cytarabine Cmax on Day 5



Source: Report JAZP-PMX-CPX351-1032_ER, Figure 4

Figure 7: Probability of Rash as a Function of Cytarabine Cmax on Day 5



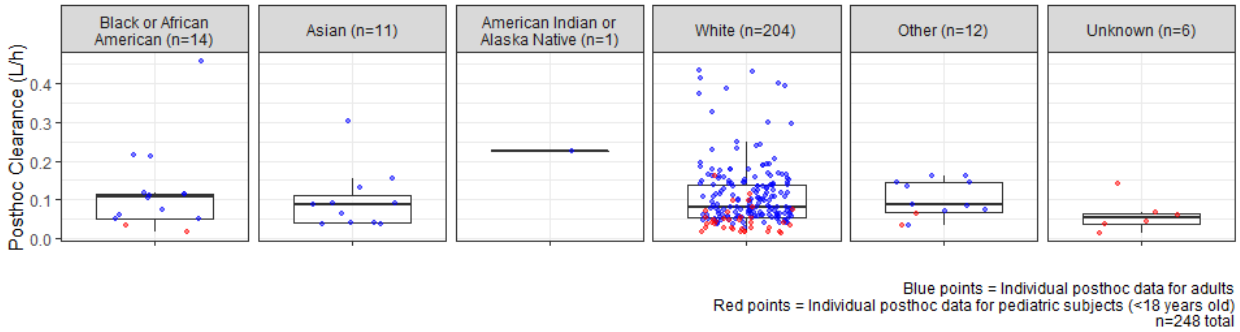
Source: Report JAZP-PMX-CPX351-1032_ER, Figure 5

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

As described above, age (1 to 81 years) does not significantly affect daunorubicin or cytarabine exposure after administration of CPX-351. In addition, sex, race (White, Black, and Asian), body weight (9 to 156 kg), body mass index (14 to 48 kg/m^2), and white blood cell count (0.2 to 111 Gi/L) had no clinically meaningful effects on the pharmacokinetics of daunorubicin and cytarabine after adjusting dose by body surface area.

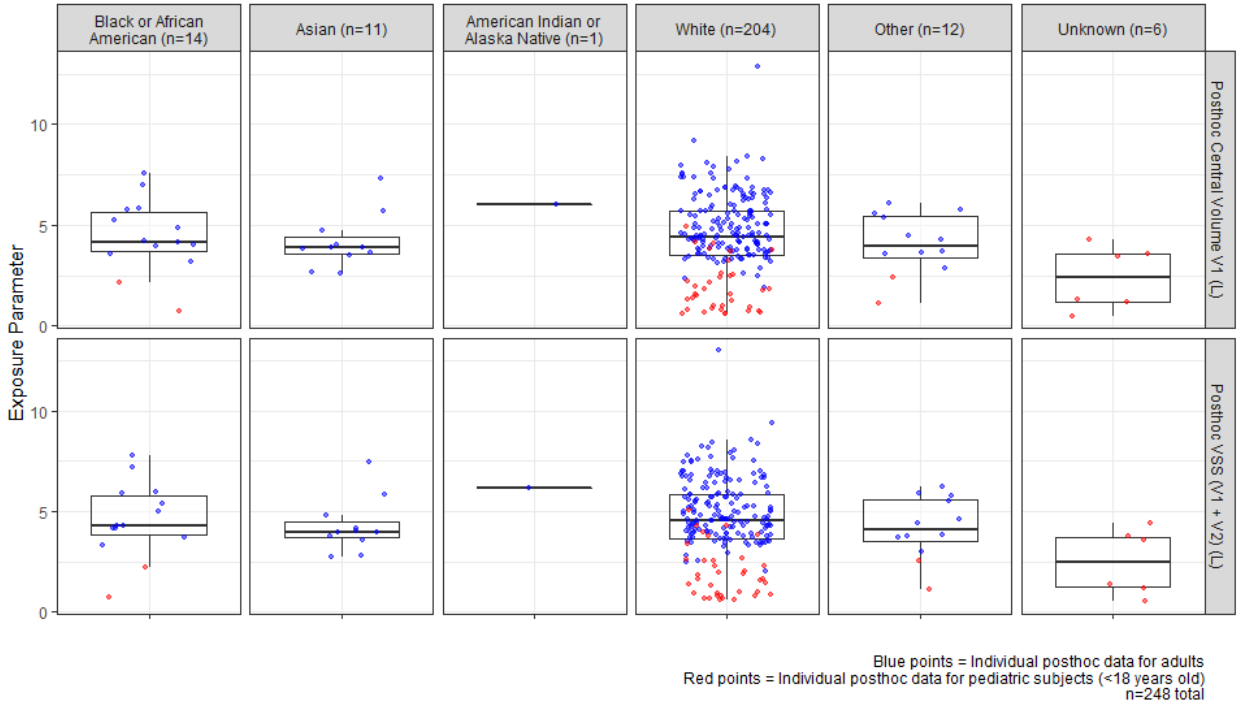
Race: The effects of race on daunorubicin and cytarabine pharmacokinetics were evaluated using the updated population PK models. Races represented were White (n=204), Black or African American (n=14), Other (n=12), Asian (n=11), and American Indian or Alaska Native (n=1). Race was unknown in 6 patients. While the number of non-White patients are limited, estimates of clearance and volume of distribution were similar across White, Black or African American, and Asian patients (**Figure 8** and **Figure 9**). There were not enough patients of other races to make conclusions on the effects of race for other racial groups.

Figure 8: Estimates of Cytarabine Clearance by Race



Source: Reviewer's Analysis

Figure 9: Estimates of Cytarabine Volume of Distribution by Race



Source: Reviewer's Analysis

To evaluate the effects of race on CPX-351 safety, adverse events were compared based on the pooled safety population of 430 patients across 7 clinical studies (AAML1421, CPX-MA-1201, CLTR0310-301, CLTR0310-206, CLTR0308-205, CLTR-0308-204, and CLTR-0305-101). Nearly all patients had at least one Grade 3 or higher adverse event. The maximum adverse event grade distribution and incidence of serious adverse events were similar across White, Black or African American, and Asian patients (**Table 2**). There were not enough patients of other races to make conclusions on the effects of race for other racial groups.

Table 2. Maximum Adverse Event Grade and Serious Adverse Events by Race – Pooled Safety Population

Race	Maximum AE Grade						Serious AE
	1	2	3	4	5	3-5	
White (n=368)	1 (0.3%)	23 (6.2%)	197 (53.5%)	75 (20.4%)	71 (19.3%)	343 (93.2%)	219 (59.5%)
Black or African American (n=28)	0	1 (3.6%)	14 (50%)	7 (25%)	6 (21.4%)	27 (96.4%)	18 (64.3%)
Other* (n=13)	0	0	8 (61.5%)	3 (23.1%)	2 (15.4%)	13 (100%)	11 (84.6%)
Asian (n=11)	0	0	7 (63.6%)	3 (27.3%)	1 (9.1%)	11 (100%)	6 (54.5%)
American Indian or Alaska Native (n=1)	0	0	1 (100%)	0	0	1 (100%)	0
Native Hawaiian or Other Pacific Islander (n=1)	0	0	1 (100%)	0	0	1 (100%)	1 (100%)
Unknown (n=8)	0	0	1 (12.5%)	5 (62.5%)	1 (12.5%)	7 (87.5%)	6 (75%)

*Other includes patients with race identified as Other or with more than one race
Source: Reviewer's Analysis

6.3.2.4 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 label includes language describing potential increased risks of toxicity when CPX-351 is used with cardiotoxic or hepatotoxic agents. Refer to the original multidisciplinary review for NDA 209401. No new information related to drug-drug interactions was included in the current sNDA.

7 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1 Table of Clinical Studies

Table 3. Clinical Trials of CPX-351

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries
Pediatric Studies				
AAML1421	Phase 1/2, single-arm dose-escalation study of CPX-351 followed by FLAG Primary endpoint: Phase 1: RP2D Phase 2: CR + CRp after Cycle 2	Cycle 1 of CPX-351: *Starting dose:* 135 Units/m^2, Days 1, 3, and 5 *Dose Level -1:* 100 Units/m^2, Days 1, 3, and 5 Cycle 2 FLAG	n = 38 Age: 1-21 years R/R AML – 1st relapse	US: 23 Canada: 2
CPM-MA-1201	Phase 1, single-arm dose-escalation study Primary endpoint: RP2D	Single cycle of CPX-351: *Starting dose:* 100 Units/m^2, Days 1, 3, and 5 *Dose Level 2:* 134 Units/m^2, Days 1, 3, and 5	n = 27 Age: 1-21 years R/R hematologic malignancies in ≥ 1st relapse *AML:* n = 23 *ALL:* n = 4	US: 1
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

Table 3. Clinical Trials of CPX-351

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries
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
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

Table 3. Clinical Trials of CPX-351

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Population	Centers/ Countries

leukemia; CMMoLAML- 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.

7.2 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- Original
- Relevant published literature
- Relevant information in the public domain

Table 4. sNDA Submission and Amendments

eCTD SDN	Received	Category	Subcategory
0334	10/7/20	Original	BLA – Efficacy Supplement
0340	11/10/20	Clinical IR	Response to Information Request
0342	11/18/20	Clinical IR	Response to Information Request
0346	12/2/20	Clinical IR	Response to Information Request
0352	12/18/20	Statistical IR	Response to Information Request
0361	2/9/21	Clinical IR	Response to Information Request

The clinical review of efficacy was based primarily on the FDA review of the original submission of NDA 209401 and an assessment of information on the biological basis of the disease for extrapolation from the adult population to pediatric patients. The Applicant submitted an ISS that included only the pediatric studies (AAML1421 and CPX-MA-1201), so the clinical review of safety was based on analyses of only the pediatric studies, and comparisons were made to the results reported in the FDA review of the adult population in original submission.

Statistical analyses by the clinical reviewer were performed using JMP 15.0 (SAS Institute, Inc., Cary, NC). All major safety analyses were reproduced or audited. Safety analyses were performed using MedDRA-Based Adverse Event Diagnostics (MAED) v1.8 (US FDA, Silver Spring, MD). Unless stated otherwise, all other p-values are unadjusted for multiplicity and should be interpreted with caution.

8 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 AAML1421

AAML1421 - A Phase 1/2 Study of CPX-351 (NSC# 775341; IND #129443) Alone Followed by Fludarabine, Cytarabine, and G-CSF (FLAG) for Children with Relapsed Acute Myeloid Leukemia (AML)

INVESTIGATIONAL PLAN

Trial Design and Endpoints

AAML1421 was a single-arm, multicenter, dose-finding, dose-expansion study of CPX-351 followed by FLAG in pediatric patients ages 1-21 years with AML in first relapse.

Other key eligibility criteria:

- Adequate cardiac function:
  - Shortening fraction ≥ 27% or ejection fraction ≥ 50%
  - Corrected QT (QTcB interval) < 500 msecs
- Excluded patients who had received > 450 mg/m^2 daunorubicin equivalents

Treatment plan:

- Phase 1 – Cycle 1 CPX-351 administered over 90 minutes on Days 1, 3, and 5

CPX-351 Dose Level	CPX-351 Dose (1 Unit = 1 mg cytarabine and 0.44 mg daunorubicin)
0	100 Units/m^2/dose
1	135 Units/m^2/dose

Source: AAML1421 Protocol

- Cycle 2 FLAG
- Intrathecal chemotherapy will be given prior to each cycle of systemic therapy.

Phase 2 expansion of RP2D on the schedule above

Primary endpoint

- Phase 1 – RP2D
- Phase 2 – ORR (CR + CRp) after 2 cycles of treatment (CPX-351 followed by FLAG)

Secondary endpoint

- CR + CRp + CRi after 1 cycle of CPX-351

Statistical Analysis Plan

Phase 1 was conducted using a modified rolling 6 design with dosing decisions depending on the number of participants enrolled, number of DLTs (CTCAE v4.0), and number of participants at risk of developing DLT (i.e. those enrolled but not yet assessable for toxicity).

Phase 2 followed a Simon two-stage design and included patients treated in Phase 1 at the RP2D:

Figure 10. AAML1421 – Simon 2-Stage Design

The Efficacy Phase is a single arm two-stage design. The following optimal Simon two-stage design will be used to test the null hypothesis that the overall response rate is ≤ 40% versus the alternative hypothesis that the response rate is ≥ 60%.

	Cumulative Number of Responses	Decision
Stage 1: Enter 12 patients	5 or fewer	Terminate the trial because the therapy is ineffective
	6-12	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 26 additional patients	18 or fewer	Conclude therapy is ineffective
	19-38	Conclude therapy is effective

If the therapy is associated with a 40% response rate (CR+CRp) after up to 2 cycles of therapy, the therapy will be identified as effective with probability 0.10. If the therapy is associated with a 60% response rate, the therapy will be identified as effective with probability 0.80.

Source: AAML1421 Protocol, Page 57

Protocol Amendments

Amendment 2: dated February 22, 2018:

- RP2D = 135 Units/m^2/dose
- AE reports must be submitted in CTCAE v5.0
- Minor updates based on updated IB for CPX-351

STUDY RESULTS

Compliance with Good Clinical Practices

The Applicant stated in Module 2.5 and in the AAML1421 Clinical Study Report in Section 5.2 that the trial was conducted in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and standard operating procedures for clinical research and development at COG.

Financial Disclosure

COG informed the applicant that disclosures for AAML1421 must be requested by regulators. However, for an application relying on PK/safety only, these were not deemed necessary. In response to IR, the Applicant conducted an internal search regarding financial arrangements and found no financial interests requiring disclosure.

Data Quality and Integrity

Data from the study AAML1421 were provided electronically with nonstandard formats. The data and analysis quality of the submission along with clarifications provided in response to information requests was acceptable to perform the review.

Patient Disposition

- First subject screened – April 26, 2016
- Primary database cutoff – June 30, 2019

At the time of database closure, all patients were off protocol therapy:

- 66% completed therapy
- 26% discontinued due to physician decision
- 8% discontinued due to treatment failure

Protocol Violations/Deviations

Per COG policy, protocol deviations were not defined in the protocol and other than deviations regarding eligibility, no other information on protocol deviations were collected. There were no reported deviations regarding eligibility.

Table of Demographic Characteristics

Table 5. AAML1421 – Demographics

	Number of Subjects, n (%)		
	Dose Finding Phase N = 6	**Efficacy Phase N = 32**	**Total N = 38**
Gender			
Male	3 (50.0)	15 (46.9)	18 (47.4)
Female	3 (50.0)	17 (53.1)	20 (52.6)
Age (years)			
n	6	32	38
Mean (SD)	13.8 (5.91)	10.0 (6.41)	10.6 (6.42)
Median	14.5	10.5	11.0
Min, Max	7, 21	1, 21	1, 21
Age Group (years)			
≥ 1 to < 2	0	3 (9.4)	3 (7.9)
≥ 2 to < 12	3 (50.0)	14 (43.8)	17 (44.7)
≥ 12 to < 18	0	10 (31.3)	10 (26.3)
≥ 18 to ≤ 21	3 (50.0)	5 (15.6)	8 (21.1)
Race			
Asian	0	2 (6.3)	2 (5.3)
Black/African American	2 (33.3)	2 (6.3)	4 (10.5)
Native Hawaiian or Other Pacific Islander	0	1 (3.1)	1 (2.6)
White	4 (66.7)	22 (68.8)	26 (68.4)
Other	0	1 (3.1)	1 (2.6)
Unknown	0	4 (12.5)	4 (10.5)
Ethnicity			
Hispanic or Latino	1 (16.7)	6 (18.8)	7 (18.4)
Not Hispanic or Latino	5 (83.3)	24 (75.0)	29 (76.3)
Unknown	0	2 (6.3)	2 (5.3)

Abbreviations: Max = maximum; Min = minimum.
Note: Percentages are based on N.

Source: AAML1421 CSR Table 3.

Other Baseline Characteristics

- The study population included 2 patients listed as “AML with myelodysplasia-related changes”.
- Although prior transplantation was allowed per protocol (≥ 3 months post alloHSCT), no data are provided regarding how many patients treated on AAML1421 had a prior transplantation.

Treatment Compliance

CPX-351 was administered by healthcare staff. In AAML1421, 100% of patients received all three doses of CPX-351 per protocol (updated in response to IR eCTD 0361). There were no dose modifications.

***Efficacy Results – Primary Endpoint**

Phase 2 – ORR (CR + CRp) after Cycle 1 CPX-351 and Cycle 2 FLAG (ITT)

- ORR (CR + CRp) = 25/38 = 65% (49, 80)
  - CR = 20/38 = 53% (36, 69)

***Efficacy Results – Secondary and Other Relevant Endpoints**

Phase 2 – ORR (CR + CRp + CRi) after Cycle 1 CPX-251 (ITT)

- ORR (CR + CRp + CRi) = 28/38 = 73% (57, 87)
  - CR = 14/38 = 38% (22, 54)

Of the 2 subjects reported to have AML with myelodysplasia-related changes (SUBJID (b) (6), (b) (6), one achieved CR and one CRp after Cycle 1.

Clinical Reviewer Comment: All efficacy data described above are based on applicant-reported outcomes. No patient-level laboratory data were available from this study to confirm response. Additionally, although AAML1421 may be considered a positive trial as designed, ORR is not an endpoint that would support approval for an AML indication.

8.1.2 CPX-MA-1201

CPX-MA-1201 - A Phase I/Pilot Study of CPX-351 for Children, Adolescents and Young Adults with Recurrent or Refractory Hematologic Malignancies

Trial Design and Endpoints

CPX-MA-1201 was a single-arm, single center, dose-escalation/expansion study of a single cycle of CPX-351 in pediatric patients and young adults with R/R hematologic malignancies.

Key eligibility criteria:

- Age:
  - Dose-exploration phase - > 12 months to 21 years
  - Expanded phase - > 12 months to 30 years
- Diagnosis of AML, ALL, or aggressive lymphoma

- AML: first or greater relapse or refractory to at least 2 courses of induction
- ALL: second or greater relapse or refractory to re-induction therapy
- Lymphoma: R/R disease for which there is no known curative therapy
- Adequate cardiac function:
    - Shortening fraction ≥ 27% or ejection fraction ≥ 50%
- Prior anthracycline exposure:
    - If no prior TBI, total previous cumulative anthracycline exposure ≤ 450 mg/m^2 daunorubicin equivalents
    - If prior TBI, total previous cumulative anthracycline exposure ≤ 300 mg/m^2 daunorubicin equivalents
- Excludes patients with history of Wilson's disease or other copper-metabolism disorder

Treatment Plan

- One cycle of CPX-351 IV over 90 minutes on Days 1, 3, and 5

Dose Level	CPX-351 (1 Unit = 1 mg cytarabine and 0.44 mg daunorubicin)
-1	67 Units/m^2/dose (i.v.), once daily on Days 1, 3, 5
1	100 Units/m^2/dose (i.v.), once daily on Days 1, 3, 5
2	134 Units/m^2/dose (i.v.), once daily on Days 1, 3, 5

Source: CPX-MA-1201 Protocol

- Intrathecal cytarabine may be administered at the treating physician's discretion prior to initiation of CPX-351.

Primary endpoint

- RP2D defined as MTD

Secondary endpoint

- ORR (CR + CRp + CRi)

Statistical Analysis Plan

The dose-exploration phase was conducted using a rolling 6 design with dosing decisions depending on the number of participants enrolled, number of DLTs (CTCAE v4.0), and number of participants at risk of developing DLT (i.e. those enrolled but not yet assessable for toxicity).

Disease response was reported descriptively.

Protocol Amendments

- Version 2: Dated 4/23/15 – Study duration increased to 4 years due to slow accrual
- Version 3: Dated 1/19/17 – Summary of dose-exploration phase added, RP2D 100

Units/m^2/dose

- Version 4: Dated 10/22/18 – CRi added to definition of OR rate ("inadvertently omitted from the protocol's original text and was discovered during the analysis of the data")

STUDY RESULTS

Compliance with Good Clinical Practices

The Applicant stated in Module 2.5 and in the CPX-MA-1201 Clinical Study Report in Section 5.2 that the trial was conducted in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and standard operating procedures for clinical research and development at CCH Medical Center in Cincinnati, Ohio.

Financial Disclosure

Form 3454 was submitted for investigators in CPX-MA-1201. In addition, the Applicant conducted an internal search regarding financial arrangements and found no financial interests requiring disclosure.

Data Quality and Integrity

Data from the study CPX-MA-1201 were provided electronically. The data and analysis quality of the submission along with clarifications provided in response to information requests was acceptable to perform the review.

Patient Disposition

- First subject screened: September 2013
- Primary database cutoff: December 2018

A total of 27 patients were treated with CPX-351 on this study (22 with 100 U, 5 with 134 U). Overall, 26/27 completed therapy and 1 discontinued prior to completion due to disease progression. Seventeen patients completed 6 months of follow-up while 10 died prior to 6-month follow-up.

Protocol Violations/Deviations

A total of 18 subjects had 27 protocol deviations. Deviations were largely recorded as "scheduled procedure" and were related to study sample collection not collected or collected outside of the prespecified windows. The remainder of reported deviations (n = 3) were related to timing or duration of CPX-351 administration (i.e. given over a longer period than 90 minutes or given 30 minutes after scheduled to begin). These deviations are unlikely to impact the

overall assessment of benefit:risk of CPX-351 in this population.

Table of Demographic Characteristics

Table 6. CPX-MA-1201 – Demographics

	Number of Subjects, n (%)					
	Dose Exploration Phase			Expanded Phase		
	100 units/m^2 N = 4	134 units/m^2 N = 5	Overall Dose Exploration Phase N = 9	100 units/m^2 N = 18	Overall CPX-351 100 units/m^2 N = 22	Total N = 27
Gender						
Male	2 (50.0)	3 (60.0)	5 (55.6)	8 (44.4)	10 (45.5)	13 (48.1)
Female	2 (50.0)	2 (40.0)	4 (44.4)	10 (55.6)	12 (54.5)	14 (51.9)
Age (yrs)						
Mean (SD)	8.3 (5.74)	8.4 (7.50)	8.3 (6.36)	5.9 (5.66)	6.3 (5.61)	6.7 (5.90)
Median	8.5	5.0	8.0	3.5	4.5	5.0
Min, Max	1, 15	2, 17	1, 17	1, 19	1, 19	1, 19
Age Group (yrs), n (%)						
≥ 1 to 2	1 (25.0)	0	1 (11.1)	3 (16.7)	4 (18.2)	4 (14.8)
≥ 2 to 12	2 (50.0)	3 (60.0)	5 (55.6)	11 (61.1)	13 (59.1)	16 (59.3)
≥ 12 to 18	1 (25.0)	2 (40.0)	3 (33.3)	3 (16.7)	4 (18.2)	6 (22.2)
≥ 18 to ≤ 21	0	0	0	1 (5.6)	1 (4.5)	1 (3.7)
Race						
White	3 (75.0)	3 (60.0)	6 (66.7)	15 (83.3)	18 (81.8)	21 (77.8)
Black/African American	0	0	0	2 (11.1)	2 (9.1)	2 (7.4)
Unknown	1 (25.0)	2 (40.0)	3 (33.3)	1 (5.6)	2 (9.1)	4 (14.8)
Ethnic Group						
Hispanic or Latino	0	1 (20.0)	1 (11.1)	2 (11.1)	2 (9.1)	3 (11.1)
Not Hispanic or Latino	4 (100)	3 (60.0)	7 (77.8)	15 (83.3)	19 (86.4)	22 (81.5)
Unknown	0	1 (20.0)	1 (11.1)	1 (5.6)	1 (4.5)	2 (7.4)

Source: CPX-MA-1201 CSR Table 4.

Other Baseline Characteristics

Of 22 patients treated at 100 U/m^2, 4 had a diagnosis of ALL and 18 had a diagnosis of AML. Of 5 patients treated at 134 U/m^2, all 5 had a diagnosis of AML. Although patients with aggressive lymphomas were eligible for enrollment, no patients with lymphoma were included on this study.

The Applicant reported that 100% of patients had prior chemotherapy, and 44% of patients with AML and 25% with ALL had received prior transplantation. One patient with AML (4%) and 3/4 (75%) with ALL had received prior radiation therapy.

Clinical Reviewer Comment: As expected per the eligibility criteria, CPX-MA-1201 included a more heterogeneous patient population compared with AAML1421. There were no data

included in the data file to allow determination of the exact number of prior therapies each patient received nor does the CSR report this information.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

CPX-351 was given by healthcare staff and compliance was not of concern. In CPX-MA-1201, 100% of patients received all three doses of CPX-351 per protocol. There were no dose modifications.

Efficacy Results – Primary Endpoint

There was no primary efficacy endpoint in this study.

***Efficacy Results – Secondary and Other Relevant Endpoints**

Applicant's descriptive assessment of response:

- Patients with AML treated at 100 U/m^2:
  - ORR (CR + CRp + CRi) = 6/18 = 33% (13, 59)
  - CR = 3/18 = 17% (4, 41)
- Patients with AML treated at 134 U/m^2:
  - CR = 2/5 = 40% (5, 85)
- All subjects with ALL received 100 U/m^2. No subjects with ALL responded to treatment.

****Clinical Reviewer Comment: CPX-MA-1201 did not include an efficacy hypothesis. All efficacy data described above are based on applicant-reported outcomes. No patient-level laboratory data were available from this study to confirm response.***

8.1.3 CLTR0310-301

CLTR0310-301 - 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.

CLTR0310-301 (Study 301; NCT01696084) was a randomized, multicenter, open-label, active-control study which compared CPX-351 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 CPX-351 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 CPX-351 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.

See the NDA 209401 Multidisciplinary Review dated 8/2/2017 for details of the study design and the efficacy and safety results in the analysis at the time of original approval. Relevant safety results are incorporated in Section 8.3. Comments on the updated results are below, and relevant efficacy outcomes are incorporated in Section 8.2.

In this sNDA submission, the applicant provided updated overall survival results from 60-month follow-up of CLTR0310-301. The applicant noted that 60-month OS was 18% for the CPX-351 arm and 8% for the 7+3 arm (HR 0.70 [95% CI: [0.55, 0.91]).

Clinical Reviewer Comment: This updated OS analysis was not alpha-controlled (b) (4)

8.1.4 Additional Studies of Treatment of Relapsed or Refractory AML

Study CLTR0308-205 was a randomized Phase 2 trial comparing CPX-351 to investigator's choice of intensive salvage therapy for patients 15-60 years old with AML in first relapse. It is described in detail in the NDA 209401 Multidisciplinary Review dated 8/2/2017. The enrolled population included 90% of patients with de novo AML and 10% with secondary AML. The study failed to meet its primary objective of improvement in OS at 1 year (b) (4)

Clinical Reviewer Comment: In general, an OS advantage is not required to support an indication for relapsed AML. CR with durability in an appropriately designed trial could support such an indication. The original review reported a similar CR rate between CPX-351 and IC (38% vs 32%, respectively). (b) (4)

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods

The applicant proposed the indication "For treatment of adults and pediatric patients aged 1 year and older with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)".

The clinical development program for CPX-351 included 5 trials in adults described in the original review. The determination of efficacy in support of the existing adult indication was based on an OS benefit for CPX-351 over 7+3 in the randomized trial CLTR0310-301. This efficacy supplement includes 2 additional single-arm trials of CPX-351 in pediatric patients with R/R AML but there are no data on the efficacy of CXP-351 as first-line treatment of t-AML or AML-MRC from adequate and well-controlled trials in a pediatric population.

Efficacy as First-Line Therapy for t-AML or AML-MRC

The efficacy of CPX-351 for the treatment of adults with newly-diagnosed t-AML or AML-MRC was established based the randomized study CLTR0310-301. The primary endpoint was OS. The observed 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, 0.90) and a 2-sided stratified long-rank p-value of 0.005, indicating a survival benefit with CPX-351 treatment. In a sensitivity analysis, a trend for improved OS was maintained when OS was censored at HSCT. The HRs were consistent on subgroup analysis by disease subtype. CR was the first alpha-controlled key secondary endpoint and was achieved by 38% in the CPX-351 arm and by 26% in the control arm (p=0.04).

As described in Section 2.1, the etiopathogeneses and natural histories of t-AML and of AML-MRC are essentially the same in adult and pediatric patients. Additionally, as described in Section 2.2, the approach to standard-of-care therapy for AML, intensive cytotoxic regimens based on daunorubicin and cytarabine, is also the same for adult and pediatric patients with AML, since there is no known difference in sensitivity of the AML cells to chemotherapy based on age rather than mutation profile. Lastly, as discussed in Section 6.3.2.2, the population PK models based on data from pediatric and adult patients treated with CPX-351 indicated that the exposures of total daunorubicin and cytarabine observed in pediatric patients were consistent with the values observed in adults given the same dose based on BSA.

Clinical Reviewer Comment: Given the biological comparability of the disease and the consistency of exposure in children and adults, efficacy may be extrapolated from the adult data to support an indication for pediatric patients ages 1 year and older with newly-diagnosed t-AML and AML-MRC using the current recommended dose.

Dose/Dose Response

There are no additional data in this supplement that address dose response for first-line treatment of t-AML or AML-MRC.

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8.2.2 Integrated Assessment of Effectiveness

The efficacy of CPX-351 for the treatment of t-AML and AML-MRC in adult patients was established based on an OS advantage over 7+3 in the pivotal trial CLTR0310-301. There are no data regarding the efficacy of CPX-351 in pediatric patients with t-AML and AML-MRC. However, CPX-351 is a liposomal formulation of the cytotoxic drugs daunorubicin and cytarabine. Based on its mechanism of action, extrapolation of the efficacy of CPX-351 from the adult data to the pediatric population is reasonable and supports clinical benefit for the treatment of pediatric patients with t-AML and AML-MRC.

8.3 Review of Safety

8.3.1. Safety Review Approach

FDA's review of safety included data from all 65 patients treated on AAML1421 and CPX-MA-1201. The safety findings presented below informed the benefit:risk analysis and changes to the USPI for this NDA efficacy supplement.

Because patients treated CPX-MA-1201 received a single cycle of CPX-351 while those in AAML1421 went on to receive subsequent treatment with FLAG in Cycle 2, the safety review focused specifically on AEs occurring during Cycle 1. Analyses below included all AEs in the ISS adae.xpt that met the following:

- Both studies – TRTEMFL = Y
- AAML1421 – AVISIT = Cycle 1
- CPX-MA-1201 – AECAT ≠ Follow up adverse events or follow up adverse events reporting (i.e. includes all AEs listed as AE treatment or reporting or SAE)

Safety analyses utilized the grouped term "infections" which was comprised of HLGTs: bacterial infectious disorders, fungal infectious disorders, infections – pathogen unspecified, and viral infectious disorders.

8.3.2. Review of the Safety Database

Overall Exposure
All patients in both studies received 100% of the prescribed dose and all 3 doses of CPX-351 per protocol.

- In CPX-MA-1201:
  - 22/27 patients received 100 U/m^2
  - 5/27 patients received 134 U/m^2
- In AAML1421, all 38 patients received 135 U/m^2.

Relevant characteristics of the safety population

Table 8. Demographics of the Safety Population

	N = 65	
Sex		
• M	31	48%
• F	34	52%
Median Age	11 years	
Range	1 - 21	
• 1 year - < 2 years	7	11%
• 2 - <12 years	33	51%
• 12 - <18 years	16	25%
• ≥ 18 years	9	14%
Race		
• White	47	72%
• Other/Unknown	10	15%
• Black	6	9%
• Asian	2	3%
Disease		
• AML	61	94%
• ALL	4	6%
Site		
• United States	63	97%
• Canada	2	3%

Source: FDA Analysis

Adequacy of the Safety Database

The safety database includes 65 pediatric patients with AML or ALL treated with CPX-351 and covers a range of pediatric age groups. Of these 65 patients, 22 were treated at the approved adult induction dose of 100 U/m^2 days 1, 3, and 5 while 43 received a higher dose of 135 U/m^2 days 1, 3, and 5.

Clinical Reviewer Comment: Overall, the demographics of the safety population are consistent with those of the intended population, and the size is adequate to assess for new safety signals in the pediatric population in the context of a drug with an established safety profile. The age range is acceptable to assess safety down to 1 year of age.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Routine laboratory monitoring of hematology, electrolytes, blood chemistry, and urine and vital sign assessments were performed by investigators for monitoring of safety but were not collected as part of the study data for either pediatric trial.

Clinical Reviewer Comment: There are some potential limitations to the available safety data from AAML1421 and CPX-MA-1201. No laboratory or vital sign data were collected; therefore, the safety analyses will rely on PT reporting and the CRFs. However, the overall safety profile of CPX-351 has been established in adults with AML and the safety profiles of its active components daunorubicin and cytarabine are well characterized in both adult and pediatric patients. The data submitted are adequate to assess the overall safety of CPX-351 in the pediatric population.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA version 21.0. The National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 4.0 was used for AAML1421 and CPX-MA-1201.

8.3.4. Safety Results

Deaths

There were no deaths within 30 days of the last dose of CPX-351 in either study. One patient died of disease progression on Day 50; there were no other deaths within 60 days of start of therapy.

FDA attempted to adjudicate all treatment-emergent deaths based on the limited narratives available in the CSRs. No deaths were considered at least possibly related to CPX-351.
In AAML1421:

- All deaths (n = 12) occurred in follow-up
- 8 were attributable to progressive AML
- 2 deaths occurred post-transplantation (1 "transplant-related mortality", 1 aGVHD post haplo)
- 2 deaths occurred in follow-up at ASTDY >300 (1 bronchopulmonary aspergillosis, 1 multiple organ failure)

In CPX-MA-1201:

- All deaths (n = 10) occurred in follow-up
- 8 deaths were attributable to disease (progression or treatment failure with or without

subsequent therapy)
- 2 deaths occurred post-transplantation (no COD provided)

Serious Adverse Events

In Cycle 1, 68% (44/65) of patients experienced an SAE. SAEs occurring in more than 2 patients were febrile neutropenia (49%), rash (9%), hypoxia and sepsis (8% each), and colitis and stridor (5% each).

Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to AEs during treatment with CPX-351 in either study.

Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs occurring during Cycle 1 in > 5% of patients treated with CPX-351 are shown below.

Table 9. Safety Population – Common (>5%) All Grade and Grade ≥ 3 TEAEs During Cycle 1 Treatment with CPX-351

Preferred Term	All Grade N = 65		Grade ≥ 3 N = 65	
	n	(%)	n	(%)
Febrile neutropenia	41	63	41	63
Rash	39	60	27	42
Infections*	29	45	27	42
Platelet count decreased	27	42	27	42
Anaemia	25	38	25	38
White blood cell count decreased	20	31	20	31
Lymphocyte count decreased	18	28	18	28
Neutrophil count decreased	14	22	14	22
Hypokalaemia	13	20	13	20
Electrocardiogram QT prolonged	10	15	0	0
Decreased appetite	8	12	8	12
Hyperglycaemia	7	11	7	11
Hypertension	7	11	0	0
Hypoxia	6	9	5	8
Ejection fraction decreased	5	8	1	2
Sinus tachycardia	5	8	0	0
Alanine aminotransferase increased	4	6	4	6

*Grouped term
Source: FDA Analysis

Clinical Reviewer comment: The TEAEs above are known adverse reactions of CPX-351 (see Vyxeos USPI). There are no new safety signals in the pediatric population.

Laboratory Findings

In CLTR0310-301, treatment with CPX-351 was associated with prolonged severe neutropenia and thrombocytopenia in the absence of active leukemia, hyponatremia, hypokalemia, hypoalbuminemia, hyperbilirubinemia, and alanine aminotransferase increases (see Vyxeos USPI). However, routine laboratory monitoring data were not collected as part of the study data for AAML1421 or CPX-MA-1201.

Clinical Reviewer Comment: The applicant confirmed in response to IR (eCTD 0361) that no laboratory data were available from AAML1421 or CPX-MA-1201 to allow for safety analyses in the pediatric population. Although laboratory AEs by PT are included in the tables above, it is known that reporting of such AEs by PT underestimates the AE rates in clinical trials (Miller, 2017; Miller, 2019). The lack of laboratory data precludes drawing any firm conclusions regarding the effects of CPX-351 on laboratory abnormalities and the serious risk of AEs with CPX-351 in the pediatric population including prolonged myelosuppression. A PMR is needed to further characterize the risk of AEs related to laboratory test abnormalities in pediatric patients with AML treated with CPX-351. Data from pediatric patients treated with both doses of CPX-351 would be of interest in order to compare safety by dose.

Vital Signs

Regular assessments of vital signs were not collected as part of study data.

A PMR to assess vital signs for infusion-related reactions was issued at the time of the original approval (PMR 3255-1). Fifty-two adults prescribed CPX-351 at the labeled dose and schedule were enrolled in an observational study to assess the incidence and severity of IRR occurring during Cycle 1. Vital signs were captured preinfusion and 5, 10, 30, 90, 120, and 180 minutes after the start of each infusion. The applicant reported only modest changes in vital sign parameters from baseline that were not considered clinically significant or indicative of AEs. The analyses provided showed minimal mean and median shifts from baseline for systolic and diastolic blood pressure, temperature, respiration rate, pulse, and oxygen saturation at the time periods tested (see Table 14.3.3.1 in CSR for CPX351-402 submitted 6/18/20, eCTD 0316). There were no IRR reported on Day 1 and one event reported starting on Day 2 (Grade 1 pyrexia: Day 2, Grade 2 shortness of breath: Day 4). No subjects discontinued due to IRR or TEAEs.

Clinical Reviewer Comment: This PMR study suggests that vital sign abnormalities indicative of IRR are not a significant concern for treatment with CPX-351.

QT/Electrocardiograms (ECGs)

In AAML1421, the Applicant reported that "While a trend towards increasing mean and median corrected QT intervals was apparent through Follow-up 1, values appeared to return to baseline by the time of Follow-up 3." QT/electrocardiogram data were not collected in CPX-MA-1201. Cardiac ARs by PT are discussed in 8.3.6 below.

Clinical Reviewer Comment: See discussion in 8.3.6 regarding the incidence of cardiac ARs by CPX-351 dose.

Immunogenicity

CPX-351 is a liposomal formulation of 2 cytotoxic drugs. Immunogenicity is not a concern with this product.

8.3.5 Analysis of Submission-Specific Safety Issues

Copper Overload

No data on copper elevations were available for AAML1421. Data collected in CPX-MA-1201 are shown below.

Table 10. CPX-MA-1201 – Serum Copper (µg/dL) Elevations

	134 U N = 5	**100 U N = 22**
Baseline • n • Median • Range	 4 127.0 96, 152	 22 133.5 64, 212
Day 5* • n • Median • Range	 5 800 800, 800	 21 800 800, 800
Completion of Course 1^ • n • Median • Range	 5 148 123, 222	 21 162 75, 210
Follow-up • n • Median • Range	 2 140 112, 168	 11 142 74, 193

Source: Modified from CSR: CPX-MA-1201 Erratum 1, Appendix 1

*Upper limit of quantitation by clinical lab assay was 800 µg/dL. Values ≥ 800 were reported as 800 µg/dL.
^Completion of Course 1 = hematologic recovery to ANC > 1 Gi/L, plt > 100 Gi/L after nadir, Day 56, initiation of subsequent chemo, or documented PD, whichever is sooner

Clinical Reviewer comment: Based on the limited data from CPX-MA-1201, copper levels in pediatric patients treated with CPX-351 appear to return to baseline by completion of Course 1 for patients treated at both dose levels, although only 5 patients were treated at the higher dose.

Cardiac Toxicity

In AAML1421:

- The applicant reports that median LVEF value "remained above 50% at all timepoints during study treatment and for most follow-up assessments. During assessments at Follow-up 3 and Follow-up 4, LVEF appeared to decrease compared with values recorded at study entry"
- 8/38 (21%) patients had LVEF ≤ 50% at some point during study
- 3 decreased LVEF SAEs:
    - Grade 3 – Cycle 1 (DLT)
    - Grade 2 – Cycle 2
    - Grade 3 – Follow-up

Cardiac ARs by PT are discussed in 8.3.6 below.

Clinical Reviewer Comment: Cardiac ARs are known toxicities of treatment with anthracyclines including CXP-351 which contains daunorubicin. See discussion in 8.3.6 regarding the incidence of cardiac ARs by CPX-351 dose.

8.3.6 Safety Analyses by Subgroups

Drug-Demographic Interactions

Tables 11 and 12 show the incidences of Common (> 5% in 2 to < 12 year age group) all-grade AR and Grade 3-4 AR, respectively, by age subgroup. In comparisons between infants and older children, there was a trend for a higher incidence of Hypoxia (29% vs 7%; p=0.06), Stridor (29% vs 3%; p=0.009), and grades 3-4 Hypoxia (29% vs 5%; p=0.03), but the results were not robust in that a decrease by as little as one patient in the infant subgroup would negate the trend. There were also differences across the age groups in laboratory test ARs, but in the absence of actual laboratory data, these differences could not be confirmed.

Table 11. Safety Population – Common ARs in Cycle 1 by Age Group

PT	1 to < 2 years n = 7	2 to < 12 years n = 33	12 to < 18 years n = 16	≥ 18 years n = 9
	%	%	%	%
Febrile neutropenia	57	66	63	56
Rash maculo-papular	57	66	56	44
Anaemia	57	45	31	11
Platelet count decreased	57	45	44	11
Infections*	57	36	50	55
Lymphocyte count decreased	57	30	25	0
White blood cell count decreased	57	30	31	1
Neutrophil count decreased	14	24	31	0
Hypokalaemia	43	21	25	0
Decreased appetite	14	15	13	0
Hypertension	0	15	13	0
Electrocardiogram QT prolonged	29	9	19	22
Hyperglycaemia	14	9	19	0
Hypoxia	29	9	6	0
Pyrexia	0	9	0	0
Sinus tachycardia	0	9	13	0
Colitis	0	6	6	0
Ejection fraction decreased	0	6	6	22
Gamma-glutamyltransferase increased	0	6	6	11
Pericardial effusion	0	6	0	0
Proteinuria	0	6	0	0
Stridor	14	6	0	0

*Grouped term
Source: FDA Analysis

Table 12. Safety Population – Common Grade 3-4 ARs in Cycle 1 by Age Group

PT	1 to < 2 years n = 7	2 to < 12 years n = 33	12 to < 18 years n = 16	≥ 18 years n = 9
	%	%	%	%
Febrile neutropenia	56	67	63	56
Rash	43	48	25	44
Anaemia	57	45	31	11
Platelet count decreased	57	45	4	11
Infections*	57	30	50	44
Lymphocyte count decreased	57	30	25	0
White blood cell count decreased	57	30	31	11
Neutrophil count decreased	14	24	31	0
Hypokalaemia	43	21	25	0

Table 12. Safety Population – Common Grade 3-4 ARs in Cycle 1 by Age Group

PT	1 to < 2 years n = 7	2 to < 12 years n = 33	12 to < 18 years n = 16	≥ 18 years n = 9
	%	%	%	%
Decreased appetite	14	15	12	0
Hyperglycaemia	14	9	19	0
Hypertension	0	9	6	0
Pyrexia	0	9	0	0
Hypoxia	29	6	6	0
Stridor	14	6	0	0
Colitis	0	6	6	0
Gamma-glutamyltransferase increased	0	6	6	11
Proteinuria	0	6	0	0

*Grouped term
Source: FDA Analysis

There were no significant differences in safety by sex (data not shown). Safety analysis by race was inconclusive given the small patient numbers in non-white subgroups.

Dose Dependency for Adverse Events

For the purposes of the analysis of safety by CPX-351 dose, the 43 patients who received 134 or 135 U/m^2 were pooled under the heading "135 U/m^2" in the analyses discussed below.

Dose Limiting Toxicities

In CPX-MA-1201, the starting dose was 100 U/m^2. No DLTs were seen at this dose, and treatment was escalated to the 134 U/m^2 dose. Two DLTs were seen at 134 U/m^2: Grade 3 headache and Grade 3 pain. As a result, the MTD/RP2D was declared to be 100 U/m^2.

In AAML1421, the starting dose was 135 U/m^2. One patient experienced a DLT of Grade 3 Ejection fraction decreased during Cycle 1. No other DLTs were observed and this dose was declared the MTD/RP2D.

Common Adverse Reactions

A comparison of adverse reactions between the 135 U/m^2 dose (n = 43) vs the 100 U/m^2 dose (n = 22) is shown below. Tables 13 and 14 show the incidences of Cycle 1 all-grade AR and Grade 3-4 AR, respectively, occurring in more than 2 patients in either dose level in order of risk difference.

Table 13. Safety Population – All Grade ARs in Cycle 1 by CPX-351 Dose

PT	135 U/m² N = 43		100 U/m² N = 22		Risk Difference (per hundred)
	n	%	n	%	
Infections*	22	51	7	32	19
Electrocardiogram QT prolonged	8	19	2	9	10
Alanine aminotransferase increased	4	9	0	0	9
Aspartate aminotransferase increased	3	7	0	0	7
Colitis	3	7	0	0	7
Epistaxis	3	7	0	0	7
Sinus tachycardia	4	9	1	5	5
Gamma-glutamyltransferase increased	3	7	1	5	2
Ejection fraction decreased	3	7	2	9	-2
Decreased appetite	4	9	4	18	-9
Hyperglycaemia	3	7	4	18	-11
Hypertension	3	7	4	18	-11
Hypophosphataemia	0	0	3	14	-14
Rash maculo-papular	23	53	16	73	-19
Hypoxia	1	2	5	23	-20
Hypokalaemia	5	12	9	41	-29
Febrile neutropenia	22	51	19	86	-35
Neutrophil count decreased	4	9	10	45	-36
Lymphocyte count decreased	4	9	14	64	-54
White blood cell count decreased	4	9	16	73	-63
Anaemia	6	14	19	86	-72
Platelet count decreased	6	14	21	95	-82

*Grouped term
Source: FDA Analysis

Table 14. Safety Population – Grade 3-4 ARs in Cycle 1 by CPX-351 Dose

PT	135 U/m² N = 43		100 U/m² N = 22		Risk Difference (per hundred)
	n	%	n	%	
Alanine aminotransferase increased	4	9	0	0	9
Aspartate aminotransferase increased	3	7	0	0	7
Colitis	3	7	0	0	7
Infections*	20	47	7	32	5
Gamma-glutamyltransferase increased	3	7	1	5	2
Rash maculo-papular	17	40	10	45	-5
Decreased appetite	4	9	4	18	-9
Hyperglycaemia	3	7	4	18	-11
Hypophosphataemia	0	0	3	14	-14

Table 14. Safety Population – Grade 3-4 ARs in Cycle 1 by CPX-351 Dose

PT	135 U/m^2 N = 43		100 U/m^2 N = 22		Risk Difference (per hundred)
	n	%	n	%	
Hypoxia	1	2	4	18	-16
Hypertension	0	0	4	18	-18
Hypokalaemia	5	12	9	41	-29
Febrile neutropenia	22	51	19	86	-35
Neutrophil count decreased	4	9	10	45	-36
Lymphocyte count decreased	4	9	14	64	-54
White blood cell count decreased	4	9	16	73	-64
Anaemia	6	14	19	86	-72
Platelet count decreased	6	14	21	95	-81

*Grouped term
Source: FDA Analysis

- Cardiac ARs over full study period:
  - All Grade QT prolongation: 19% vs 10%
    - No Grade ≥ 3 events reported during Cycle 1
    - One Grade 3 event reported in follow-up (Day 166) in a patient who received 135 U/m^2
  - All Grade EF decrease: 12% vs 14%
    - Grade 3 EF decrease reported only at the 135 U/m^2 dose
      - One report during Cycle 1 (DLT in AAML1421)
      - One patient with new onset G3 EF decrease in follow-up (Day 256)
  - Total Grade 3 cardiac ARs: 7% vs 0%
- No conclusions can be drawn regarding hematologic toxicities by dose
  - Data on time to count recovery not available

Clinical Reviewer Comment:

- ***Notable adverse reactions reported at a higher incidence with the 135 U/m^2 dose compared to the 100 U/m^2 dose included cardiac ARs and infections.***
  - ***Although the cardiac ARs reported at both doses were largely Grade 1-2 events, Grade 3 events were reported only in patients treated at the 135 U/m^2 dose (7%).***
  - ***Infections were more common in patients treated at the higher dose and almost all reports were Grade ≥ 3. These were reported as a mix of PTs falling largely under HLGT: Infections – pathogen unspecified.***
- ***Rashes were reported at a higher incidence with the 100 U/m^2 dose; however, reports of rashes (any grade) were collected specifically as an AESI in CPX-MA-1201 but not in AAML1421.***

Most of the remaining ARs reported were for laboratory or vital sign abnormalities. Liver function test elevations were reported at a higher incidence with the 135 U/m^2 dose, and various laboratory abnormalities including all hematologic ARs were reported at a higher

incidence with the 100 U/m^2 dose. In the absence of laboratory data, none of these observations can be confirmed. However, a lower dose of a cytotoxic therapy would not reasonably be expected to cause a higher rate of myelosuppression than a higher dose of the same drug (especially in the context of a higher infection rate with the higher dose); some of these differences may be due in part to differences in AE reporting between trials.

As discussed in 8.3.4, the safety profile in the pediatric population is similar to that in adults treated with CPX-351 in CLTR0310-301. However, these analyses indicate that there are increased risks for cardiac toxicity and high-grade infections at the 135 U/m^2 dose compared with the 100 U/m^2 dose. In the absence of robust data demonstrating that the higher dose is required for efficacy, the benefit:risk of the 135 U/m^2 dose cannot be considered positive for the pediatric population. The data support 100 U/m^2 as the pediatric dose for the proposed indication.

8.3.7 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Safety in the postmarket setting was evaluated by an Empirica search of safety reports by PT or narrow SMQ. Events reported at an EBGM ≥ 2 with threshold of EB05 > 1 indicated potential associations between CPX-351 and multiple known ARs. These included shock, infections, leukemia, cytopenias and myelosuppression, rashes, edema, hemorrhagic events, cardiac ARs, and liver dysfunction.

In 2019, there were also 9 reports of metabolic encephalopathy which was not observed in the original review. However, at least 5 of the reports appear to refer to the same case (FR-JAZZ-2019-FR-013983). Another 3 reports refer to an additional single case based on drug start/end dates for Vyxeos, hydrocortisone, and various antibiotics. Minimal details were included in either narrative. The last case describes a 73-year-old woman who was diagnosed with metabolic encephalopathy 12 days after her last dose of salvage Vyxeos. The event occurred in the setting of current or recent intubation and ICU care for respiratory distress with a subsequent report of hepatic cytolysis with "labs increased to 7 X ULN". There is insufficient information in these 3 cases to determine if metabolic encephalopathy represents a safety signal for CPX-351.

No other new safety findings were identified.

Expectations on Safety in the Postmarket Setting

In the United States, use of CPX-351 for the treatment of pediatric patients in the postmarket setting will largely fall under the current COG frontline AML trial AAML1831. Overall safety in the postmarket setting is expected to be similar to that observed in AAML1421 for patients 1 year and older. The safety of off-label use in pediatric patients < 1 year old is unclear.

8.3.8 Integrated Assessment of Safety

The safety profile of CPX-351 has been established in adult trials, and there are no new safety signals in the overall pediatric population or by age subgroup compared with the adult data which supported the 2017 approval. In AAML1421 and CPX-MA-1201, there were no deaths within 30 days of the last dose of CPX-351 and no discontinuations or CPX-351 dose modifications due to AEs. Although laboratory AEs by PT were included in the safety analyses, no laboratory data were available from either pediatric study to confirm and characterize the risks of AEs related to laboratory test abnormalities including prolonged myelosuppression in the pediatric population.

Safety by CPX-351 dose:

- Serum copper levels were reported only in CPX-MA-1201 and resolved to near-baseline by end of Course 1 regardless of dose.
- Higher incidence of Grade 3 cardiac ARs (QT prolongation and EF decreases) in patients treated with the 135 U/m^2 dose compared with the 100 U/m^2 dose (7% vs 0%)
- Higher incidence of Grade ≥ 3 infections in patients treated with the higher dose (44% vs 32%)

The overall safety profile at the recommended dose in the pediatric population is similar to that established in adults and generally supports a positive benefit:risk for the use of CPX-351 in pediatric patients with t-AML and AML-MRC who are expected to have a poor prognosis. However, the limitations of the data available in this submission including the lack of laboratory data merit a PMR to further characterize the risk of AEs related to laboratory test abnormalities in pediatric patients with AML treated with CPX-351. Due to the fact that these studies are completed, collection of such data cannot be accomplished, and no further studies of this dose is planned in the pediatric population at this time.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

- Extension of the existing approved indication for the treatment of t-AML and AML-MRC in adults to include pediatric patients 1 year and older is based on extrapolation of efficacy from the adult pivotal trial CLTR0310-301 and safety data from the two pediatric trials.
- [redacted] (b) (4)
- The applicant's analysis of OS at 60-month follow-up from CLTR0310-301 was not alpha-controlled [redacted] (b) (4)

8.5 Conclusions and Recommendations

The review team recommends regular approval of this efficacy supplement with revision of the indication 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.

The review team recommends the current regimen as the pediatric dose, recommends against (b) (4) in Section 8.4 of labeling, and recommends against (b) (4).

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

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

10 PEDIATRICS

The Applicant was granted Orphan Designation for CPX-351 for the treatment of patients with AML and is therefore exempt from a pediatric assessment under the Pediatric Research Equity Act (PREA). Safety data for the use of CPX-351 for treatment of AML in pediatric patients ages 1 years and older were included in this submission. There are no data on the safety of CPX-351 in pediatric patients less than 1 year of age. See Section 8.2.2 about extrapolation of efficacy from adults to pediatric patients for the t-AML and AML-MRC indication.

On August 28, 2020, the Agency issued a Written Request for studies to investigate the potential use of CPX-351 in the treatment of AML in pediatric population. These studies were requested to provide data to determine a safe and appropriate pediatric dose and to determine the efficacy of CPX-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 Written Request included three pediatric clinical studies. Data from Study 1 (AAML1421) and Study 2 (CPX-MA-1201) were included in this sNDA submission. Study 3 (AAML1831) is an ongoing Children's Oncology Group Phase 3 randomized trial in patients less than 22 years of age with newly-diagnosed de novo AML comparing gemtuzumab ozogamicin (GO) + CPX-351 vs GO + standard therapy (daunorubicin + cytarabine) (b) (4) Reports for this study are anticipated on or (b) (4).

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
1. Indications and Usage	The Applicant proposed including pediatric patients 1 year and older to the indication of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	FDA agreed with minor edits to the order of the language.
2.1 Recommended Dosage	The Applicant proposed (b) (4)	(b) (4) the data for the pediatric population was extrapolated from the adult trial supporting the original approval. (b) (4) .
2.3 Preparation and Handling Instructions	The Applicant proposed additional bullets describing stability of reconstituted product, as well as instruction that diluted infusion solution must be immediately infused following the up to 4-hour stability period.	FDA edited this subsection to clarify that users need to reconstitute and further dilute Vyxeos prior to infusion. Separate headings were adding to differentiate the Reconstitution and Dilution sections. Additional language was added to ensure that users are made aware that reconstituted product in the vial and reconstituted product which has been diluted into an infusion solution are stable for a

		total of 4 hours, not for 4 hours each, when stored at 2^0C to 8^0C.
8.4 Pediatric Use	The Applicant updated the Pediatric Use subsection with information establishing efficacy in pediatric patients 1 year and older derived from data from one adequate and well-controlled study in adults with safety data from two single-arm trials which included pediatric patients greater than 1 year in patients with t-AML or AML MRC.	FDA agreed that the efficacy and safety data are sufficient to include an indication for the treatment of t-AML or AML MRC for pediatric patients greater than 1 year and noted that no new safety signals were observed in pediatric patients in the two single-arm studies.
	(b) (4)	
	The applicant included pharmacokinetic data in pediatric and young adults (1-21 years of age)	FDA moved this information to section 12.3.
12.3 Pharmacokinetics	The Applicant did not propose edits to this subsection	FDA included information in a new pediatric section that exposures of total daunorubicin and cytarabine observed in pediatric patients were within values observed in adults given the same dose based on body surface area (BSA). A geriatric section was added to describe that the exposures of total daunorubicin and cytarabine observed in patients greater than age 65 were within the values observed in patients aged 18-64 given the same dose based on BSA.

14 Clinical Studies	(b) (4)

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.

14 APPENDICES

14.1 References

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14.2 Financial Disclosure

As noted in Section 8.1, this supplement relies only on PK and safety data from AAML1421 and CPX-MA-1201. The applicant conducted an internal search regarding financial arrangements for these studies and found no financial interests requiring disclosure. Efficacy in this supplement is extrapolated from CLTR0310-301 and financial disclosures for this study were reviewed in the NDA 209401 Multidisciplinary Review dated 8/2/2017.

Covered Clinical Study (Name and/or Number): AAML1421, CPX-MA-1201

Was a list of clinical investigators provided:	Yes x	No ☐ (Request list from Applicant)
Total number of investigators identified: ___		
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)): 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)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes	No (Request explanation from Applicant)

14.3 Nonclinical Pharmacology/Toxicology

None.

14.4 OCP Appendices

14.4.1 Pharmacometrics Review

1. Population PK Analysis

1.1 Population PK Summary

The Applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the final cytarabine and final daunorubicin population PK models are adequate in characterizing the PK profile of cytarabine and daunorubicin in adults and pediatric subjects down to 1 year of age. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. Due to the liposomal formulation of the drug, liposomal cytarabine and liposomal daunorubicin have similar PK as expected and the population PK review will primarily focus on the final cytarabine model.

1.2 Introduction

The primary objectives of Applicant's analysis were to:

- Perform a population PK analysis of cytarabine and daunorubicin in children, adolescents and young adults with AML in study AAML1421 and CPX-MA-1201.
- Assess sources of variability in exposure.
- Support dosing in pediatric patients with AML.

1.3 Applicant's Population PK Analysis

1.3.1 Data

The analyses were based on cytarabine and daunorubicin PK concentration data from 5 clinical studies. The study design, study population, and timing of blood samples varied among the 5 studies. Brief descriptions of the studies included are presented in **Table 15.**

PK data from adults (Study CLTR0305-101, Study CLTR0310-206, and Study CLTR0310-301) and PK data from children, adolescents, and young adults (Study CPX-MA-1201 and Study AAML-1421) were pooled into one population PK dataset for each drug molecule to develop the base model and final covariate model.

The final cytarabine NONMEM data file for analysis contained 2490 PK observations from 250 subjects. The final daunorubicin NONMEM data file for analysis contained 2469 PK observations from 250 subjects. All subjects with cytarabine PK observations had daunorubicin PK observations and vice versa.

Table 15. Summary of Clinical Studies Included in Population PK Analysis

Study and Description	Subjects in popPK Dataset	Cytarabine PK Samples	Daunorubicin PK Samples	Median Age (Max-Min)	Disease state(s)	Doses
CLTR0305-101 Phase 1 dose escalation study	38	875	875	62.5 years (24 – 81)	RR-AML (n=33), RR-ALL (n=3), MDS (n=2)	3, 6, 12, 24, 32, 43, 57, 76, 100, and 135 u/m²
CLTR0310-206 Phase 2 PKPD study	26	585	566	67.0 years (37 – 80)	AML-MRC (n=7), RR-AML (n=13), de novo AML (n=6)	100 u/m²
CLTR0310-301 Pivotal Phase 3 safety and efficacy trial	131	592	592	68.0 years (60 – 75)	AML-MRC (n=95), t-AML (n=26), AML-CMMoL (n=10)	100 u/m²
CPX-MA-1201 Phase 1 pilot with dose exploration phase + expanded phase	27	269	269	5.0 years (1 – 19)	RR-AML (n=23), RR-ALL (n=4)	100 u/m² (n=22) and 135 u/m² (n=5)
AAML-1421 Phase 1/2 safety, efficacy, and PK study	28	169	167	13.0 years (1 – 21)	RR-AML (n=28)	135 u/m²
Total	250	2490	2469			

Source: Reviewer Analysis of Applicant's Datasets and Table 1, Response to FDA Information Request 10 Question 4

Table 16 and Table 17 provide summary statistics of the baseline demographic covariates in the analysis dataset.

Table 16. Summary of Baseline Characteristics in the PK Population - Categorical Data

Covariate	Sub-Population	Study ID					Overall
		305-101	310-206	310-301	CPX-MA-1201	AAML1421	
Study Population	Children, Adolescents and Young Adults	-	-	-	27(100.0%)	28(100.0%)	55(22.0%)
	Adults	38(100.0%)	26(100.0%)	131(100.0%)	-	-	195(78.0%)
Age Categories	1-5 years	-	-	-	16 (59.3%)	6 (21.4%)	22 (8.8%)
	6-11 years	-	-	-	4 (14.8%)	6 (21.4%)	10 (4.0%)
	12-17 years	-	-	-	6 (22.2%)	8 (28.6%)	14 (5.6%)
	≥18 years	38 (100.0%)	26 (100.0%)	131(100.0%)	1 (3.7%)	8 (28.6%)	204 (81.6%)
Age Groups	Pediatrics (1-17 years)	-	-	-	26 (96.3%)	20 (71.4%)	46 (18.4%)
	Adults (≥18 years)	38 (100.0%)	26 (100.0%)	131(100.0%)	1 (3.7%)	8 (28.6%)	204 (81.6%)
Bilirubin Category	Not Recorded	-	-	-	27 (100.0%)	28 (100.0%)	55 (22.0%)
	<1.2 mg/dL	37 (97.4%)	23 (88.5%)	119 (90.8%)	-	-	179 (71.6%)
	1.2 - 3 mg/dL	1 (2.6%)	3 (11.5%)	12 (9.2%)	-	-	16 (6.4%)
Formulation	Frozen	38 (100.0%)	-	-	-	-	38 (15.2%)
	Lyophilized	-	26 (100.0%)	131 (100.0%)	27 (100.0%)	28 (100.0%)	212 (84.8%)
Phase	Phase 1	38 (100.0%)	-	-	27 (100.0%)	28 (100.0%)	93 (37.2%)
	Phase 2	-	26 (100.0%)	-	-	-	26 (10.4%)
	Phase 3	-	-	131 (100.0%)	-	-	131 (52.4%)
Race	White	32 (84.2%)	25 (96.2%)	108 (82.4%)	21 (77.8%)	20 (71.4%)	206 (82.4%)
	Black	2 (5.3%)	1 (3.8%)	6 (4.6%)	2 (7.4%)	3 (10.7%)	14 (5.6%)
	Asian	4 (10.5%)	-	6 (4.6%)	-	1 (3.6%)	11 (4.4%)
	Other	-	-	11 (8.4%)	-	2 (7.1%)	13 (5.2%)
	Unknown	-	-	-	4 (14.8%)	2 (7.1%)	6 (2.4%)
Renal Function	Not Recorded	-	-	-	-	28 (100.0%)	28 (11.2%)
	CRCL ≥90 mL/min	14 (36.8%)	12 (46.2%)	57 (43.5%)	20 (74.1%)	-	103 (41.2%)
	CRCL 60 to <90 mL/min	20 (52.6%)	8 (30.8%)	55 (42.0%)	7 (25.9%)	-	90 (36.0%)
	CRCL 30 to <60 mL/min	3 (7.9%)	6 (23.1%)	19 (14.5%)	-	-	28 (11.2%)
	CRCL 15 to <30 mL/min	1 (2.6%)	-	-	-	-	1 (0.4%)
Sex	Male	26 (68.4%)	14 (53.8%)	79 (60.3%)	13 (48.1%)	16 (57.1%)	148 (59.2%)
	Female	12 (31.6%)	12 (46.2%)	52 (39.7%)	14 (51.9%)	12 (42.9%)	102 (40.8%)

CRCL = creatinine clearance

Source: Table 2, Applicant's Population PK Analysis

Table 17. Summary of Baseline Characteristics in the PK Population - Continuous Data

Covariate	Statistic	Study ID					Overall
		305-101	310-206	310-301	CPX-MA-1201	AAML1421	
Age (years)	n	38	26	131	27	28	250
	Mean (CV%)	59.3 (25.5%)	65.2 (14.3%)	67.8 (6.3%)	6.7 (87.9%)	11.8 (55.3%)	53.4 (46.7%)
	Median (Min-Max)	62.5 (24-81)	67.0 (37-80)	68.0 (60-75)	5.0 (1-19)	13.0 (1-21)	65.0 (1-81)
BSA (m^2)	n	38	26	131	27	28	250
	Mean (CV%)	1.92 (16.7%)	1.97 (13.1%)	1.95 (12.6%)	0.96 (53.1%)	1.43 (42.7%)	1.78 (26.9%)
	Median (Min-Max)	1.94 (1.26-2.8)	1.94 (1.32-2.67)	1.95 (1.45-2.64)	0.74 (0.44-2.09)	1.55 (0.45-2.75)	1.89 (0.44-2.8)
Body Weight (kg)	n	38	26	131	27	28	250
	Mean (CV%)	79 (29.4%)	83.0 (21%)	81.4 (21.3%)	29.7 (78.3%)	53.6 (62.6%)	72.5 (37.6%)
	Median (Min-Max)	76.7 (38.9-156.5)	82.2 (41.9-133.3)	79.9 (48.9-138.9)	18.0 (9.1-90.4)	54.2 (9.4-145.3)	76.1 (9.1-156.5)
ALP (U/L)	n	38	26	131			195
	Mean (CV%)	112.9 (61.9%)	77.3 (46.4%)	82.1 (54.4%)	No Records	No Records	87.5 (58.2%)
	Median (Min-Max)	87.5 (34-319)	67.5 (32-164)	69.0 (21-284)			72.0 (21-319)
ALT (U/L)	n	38	26	131	27		222
	Mean (CV%)	41.8 (77.6%)	31.1 (98.9%)	29.9 (84.5%)	52.0 (89.2%)	No Records	34.8 (89.7%)
	Median (Min-Max)	28 (15-151)	20.0 (9-153)	23.0 (3-139)	40.0 (22-219)		25.0 (3-219)
AST (U/L)	n	38	26	131			195
	Mean (CV%)	34.6 (55.1%)	23.5 (52.6%)	25.8 (62.6%)	No Records	No Records	27.2 (61.2%)
	Median (Min-Max)	28 (12-100)	19.5 (9-65)	22.0 (5-115)			23.0 (5-115)
Total Bilirubin (mg/dL)	n	38	26	131			195
	Mean (CV%)	0.64 (49.4%)	0.60 (55.2%)	0.66 (60.9%)	No Records	No Records	0.65 (58.1%)
	Median (Min-Max)	0.60 (0.2-1.8)	0.55 (0.2-1.4)	0.50 (0.1-2.5)			0.60 (0.1-2.5)
Direct Bilirubin (mg/dL)	n				27		27
	Mean(CV%)	No Records	No Records	No Records	0.1 (59.8%)	No Records	0.1 (59.8%)
	Median(Min-Max)				0.1 (0.1-0.4)		0.1 (0.1-0.4)
Creatinine Clearance (mL/min)	n	38	26	131	27		222
	Mean (CV%)	90.1 (39.3%)	96.5 (46.8%)	91.3 (34.1%)	121.2 (33.4%)	No Records	95.3 (37.8%)
	Median (Min-Max)	79.6 (27.5-171.8)	86.4 (42.3-211.7)	85.8 (38.6-177.8)	114 (62.2-229.6)		87.5 (27.5-229.6)
WBC (10^9/L)	n	38	26	131	27	27	249
	Mean (CV%)	10.3(157.1%)	11.9(204.5%)	9.3(153.3%)	10.0(199.6%)	9.0(148%)	9.8(167.1%)
	Median (Min-Max)	3.2(0.2-68.1)	3.7(0.7-110.9)	3.4(0.3-86.4)	1.9(0.2-73.9)	3.8(1-62.4)	3.4(0.2-110.9)

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, BSA: body surface area, CV: coefficient of variation, Max: maximum, Min: minimum, n: number of subjects, WBC: white blood cells

Note: The WBC value for ID AAML1421-AL013-852842 (750 10^9/L) was excluded from descriptive statistics.

Source: Table 3, Applicant's Population PK Analysis

1.3.2 Cytarabine Base Model

The base model was a two-compartment PK model with first-order elimination from the central compartment. Interindividual variability was applied to the parameters of apparent clearance (CL/F) and apparent central volume of distribution (Vc/F). The effect of BSA centered over 1.9 m^2 was included with an estimated allometric exponent on CL/F and Vc/F. The base model also included a bilirubin effect on CL/F where total bilirubin was centered over 0.6 mg/dL with an estimated allometric exponent. Subjects without a recorded bilirubin were assigned an imputed bilirubin of 0.6 mg/dL, which effectively negated any bilirubin effect for those subjects. As shown in Table 17, this means that the bilirubin only affected individual estimated PK parameters of the adult subjects because total bilirubin was not recorded in Study CPX-MA-1201 nor Study AAML-1421.

1.3.3 Cytarabine Covariate Analysis

Covariate-versus-ETA plots from the base model output were visually inspected for possible trends to determine which covariates would be investigated for development of the final model. Age (continuous), age group (1 - <18 years versus 18+ years), and study (three adult studies CLTR0305-101, CLTR0310-206, and CLTR0310-301 versus two pediatric/young adult studies AAML-1421 and CPX-MA-1201) were investigated for effects on CL/F in NONMEM. Age group and study were also investigated for effects on Vc/F.

1.3.4 Cytarabine Final Model

The final model was a two-compartment PK model with first-order elimination from the central compartment. Interindividual variability was applied to the parameters of CL/F and Vc/F. The effect of BSA centered over 1.9 m^2 was included with an estimated allometric exponent on CL/F and Vc/F. The final model also included a bilirubin effect on CL/F where total bilirubin was centered over 0.6 mg/dL with an estimated allometric exponent. Because the same cytarabine dataset was used to develop the base and final cytarabine models, bilirubin was still imputed as 0.6 mg/dL for all subjects without recorded bilirubin and thus bilirubin only affected individual estimated CL/F in adult subjects.

The only difference in the structure of the final cytarabine model compared to the base model was the addition of a Study effect which decreased CL/F by 27.6% and decreased Vc/F by 17.8% for subjects in Studies CPX-MA-1201 and AAML-1421.

The Applicant's parameter estimates for the final model are listed in Table 18. The prediction-corrected Visual Predictive Check (pcVPC) plot for the final model is shown in Figure 11.

Table 18. Applicant Cytarabine Final Population PK Model – Parameter Estimates

Parameter	Units	Estimate	SE	RSE%	95% CI	Shrinkage	Equation
OFV		-4306.6935					
CL	L/h	0.101	0.00380	3.7%	0.0939 - 0.109		$CL = tvCL \cdot \exp(\eta CL)$
BSA_CL		0.948	0.0418	4.4%	0.866 - 1.03		$\times (BSA/1.9)^{BSA\_CL}$
Bili_CL		0.245	0.0254	10.4%	0.195 - 0.295		$\times (Bilirubin/0.6)^{Bili\_CL}$
Stud_CL		-0.323	0.0372	11.5%	-0.396 - -0.250		× exp(Stud_CL) if Study 1201 or 1421
Vc	L	4.76	0.0943	2.0%	4.58 - 4.95		$Vc = tvVc \cdot \exp(\eta Vc)$
BSA_Vc		1.26	0.0460	3.6%	1.17 - 1.36		$\times (BSA/1.9)^{BSA\_Vc}$
Stud_Vc		-0.196	0.0456	23.3%	-0.285 - -0.106		× exp(Stud_Vc) if Study 1201 or 1421
Q	L/h	0.00176	0.000594	33.7%	0.000600 - 0.00293		$Q = tvQ \cdot \exp(\eta Q)$
BSA_Q		1.00	fixed	-	-		$\times (BSA/1.9)^{BSA\_Q}$
Vp	L	0.133	0.0349	26.2%	0.0650 - 0.202		$Vp = tvVp \cdot \exp(\eta Vp)$
BSA_Vp		1.00	fixed	-	-		$\times (BSA/1.9)^{BSA\_Vp}$
LogErr		0.161	0.00674	4.2%	0.147 - 0.174	12.5%	$\ln(Cobs) = \ln(Cpred) + LogErr \cdot \exp(\eta LogErr)$
BSV_CL		0.270(55.6%)	0.0542	20.1%	0.163 - 0.376	3.3%	$\omega^2 CL$
BSV_Vc		0.0528(23.3%)	0.0115	21.7%	0.0303 - 0.0753	9.5%	$\omega^2 Vc$
BSV_Q		0.00	fixed	-	-	-	$\omega^2 Q$
BSV_Vp		0.00	fixed	-	-	-	$\omega^2 Vp$
BSV_LogErr		0.416(71.8%)	0.0703	16.9%	0.278 - 0.553	13.6%	$\omega^2 LogErr$

CL = clearance; BSA_CL = BSA effect on CL; Bili_CL = bilirubin effect on CL; Stud_CL = study effect on CL

Vc = central volume of distribution; BSA_Vc = BSA effect on Vc; Stud_Vc = study effect on Vc

Q = peripheral clearance; BSA_Q = BSA effect on Q

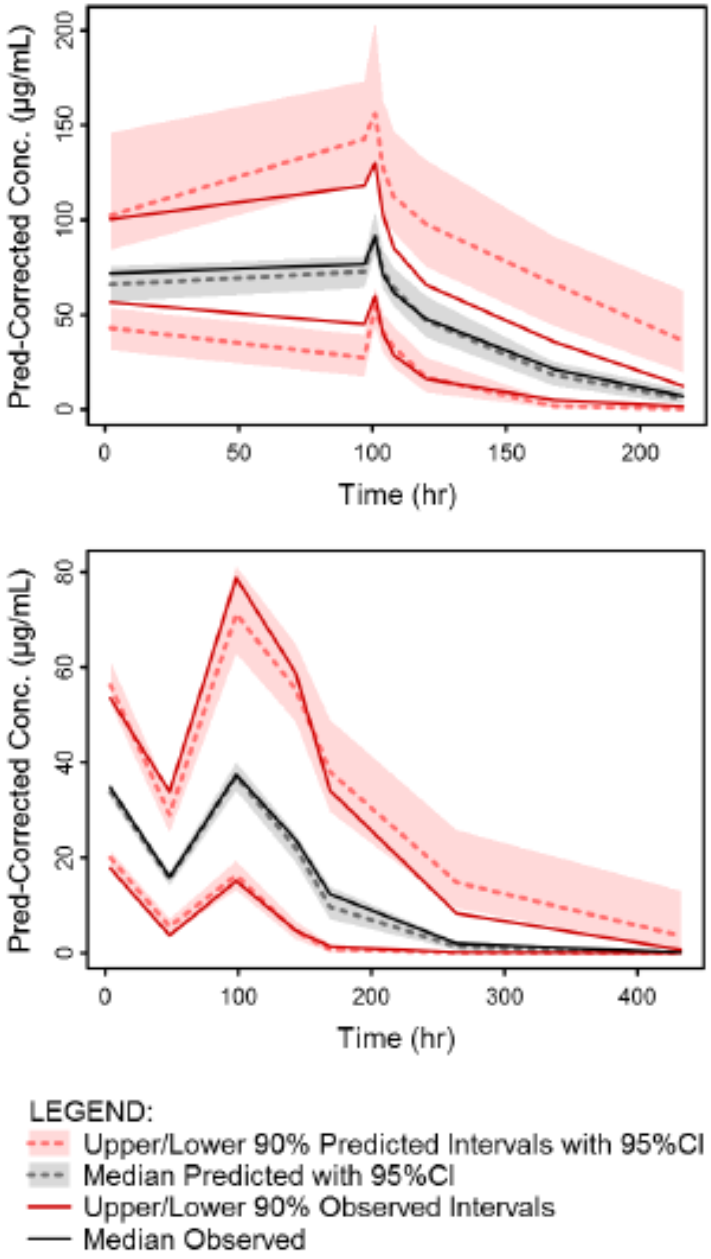
Vp = peripheral volume of distribution; BSA_Vp = BSA effect on Vp

OFV = objective function value; BSV = between-subjects variability; CI = confidence intervals; RSE = relative standard error; SE = standard error

NOTE: BSV% were calculated as $(\exp(\omega^2)-1)^{0.5}$

Source: Table 12.25, Applicant's Population PK Analysis

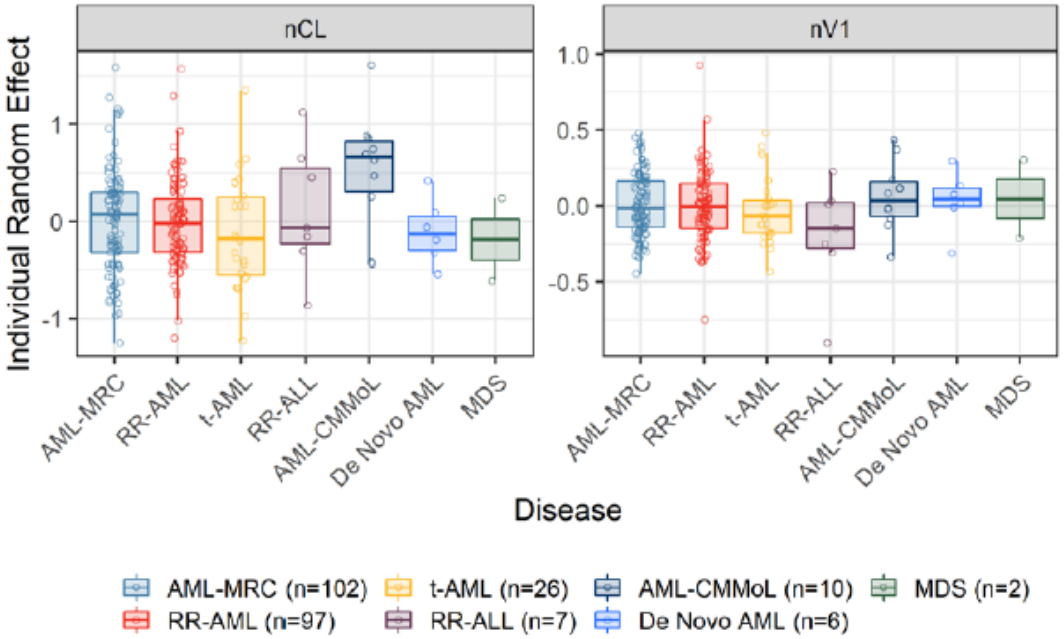
Figure 11. Goodness-of-Fit for Final Model of Cytarabine: Population and Individual Predicted vs. Observed Concentrations in Children, Adolescents and Young Adults (Top) and Adults (Bottom)



Source: Figure 3, Applicant's Population PK Analysis

Individual disease state (t-AML, AML-MRC, or otherwise) was also assessed for potential parameter effects although there were no significant trends or relationships identified. Individual estimates of cytarabine CL/F and Vc/F are presented by disease state in Figure 12.

Figure 12. Relationships Between Cytarabine PK Parameters and Disease Type in Final Cytarabine Population PK Model



Source: Figure 1, Applicant's Response to FDA Information Request 10 Question 4

Reviewer Comments

The Reviewer's parameter estimates for the final model are listed in Table 19. The goodness-of-fit plots for the final model are in ***Figure 13****. Key goodness-of-fit plots grouped by age category are in* ***Figure 14*** *and indicate acceptable fit with no significant differences in fit across age groups. Key goodness-of-fit plots grouped by study number are in Figure 15 and indicate acceptable fit with no significant differences in fit across the five studies.*

The SE and RSE on bilirubin effect (BILICL) and study effect on clearance (STUDCL) were higher in the Reviewer's model output (BILICL RSE = 24.5%; STUDCL RSE = 17.3%) compared to the Applicant's model output (BILICL RSE = 10.4%; STUDCL RSE = 11.5%). The 95% CI for BILICL and STUDCL were also wider in the Reviewer's model output (BILICL 95% CI 0.128 - 0.364; STUDCL 95% CI -0.422 - -0.208) compared to that of the Applicant's model output (BILICL 95% CI 0.195 - 0.295; STUDCL 95% CI -0.396 - -0.250). These differences SE and RSE were relatively minor and did not change any conclusions drawn from the model. Other than that, there were no discrepancies between the Applicant's final cytarabine model and Reviewer analysis.

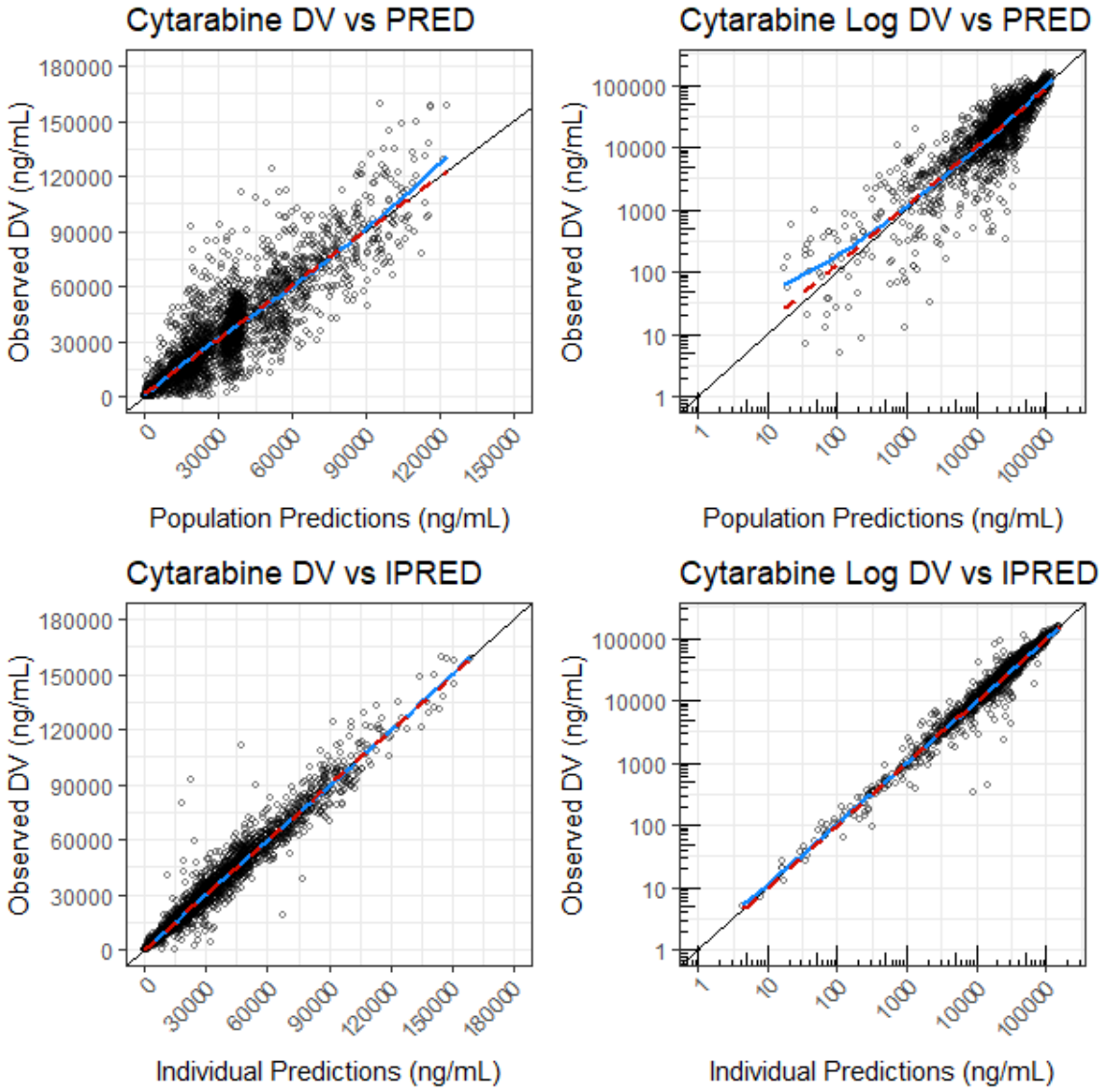
Overall, based on the GOF plots in ***Figure 13,*** *the age-category-stratified GOF plots in* ***Figure 14,*** *and the study-stratified GOF plots in Figure 15****,*** *the final cytarabine population PK model appears adequate in characterizing the PK profile of liposomal cytarabine in adults as well as pediatric subjects down to 1 year of age.*

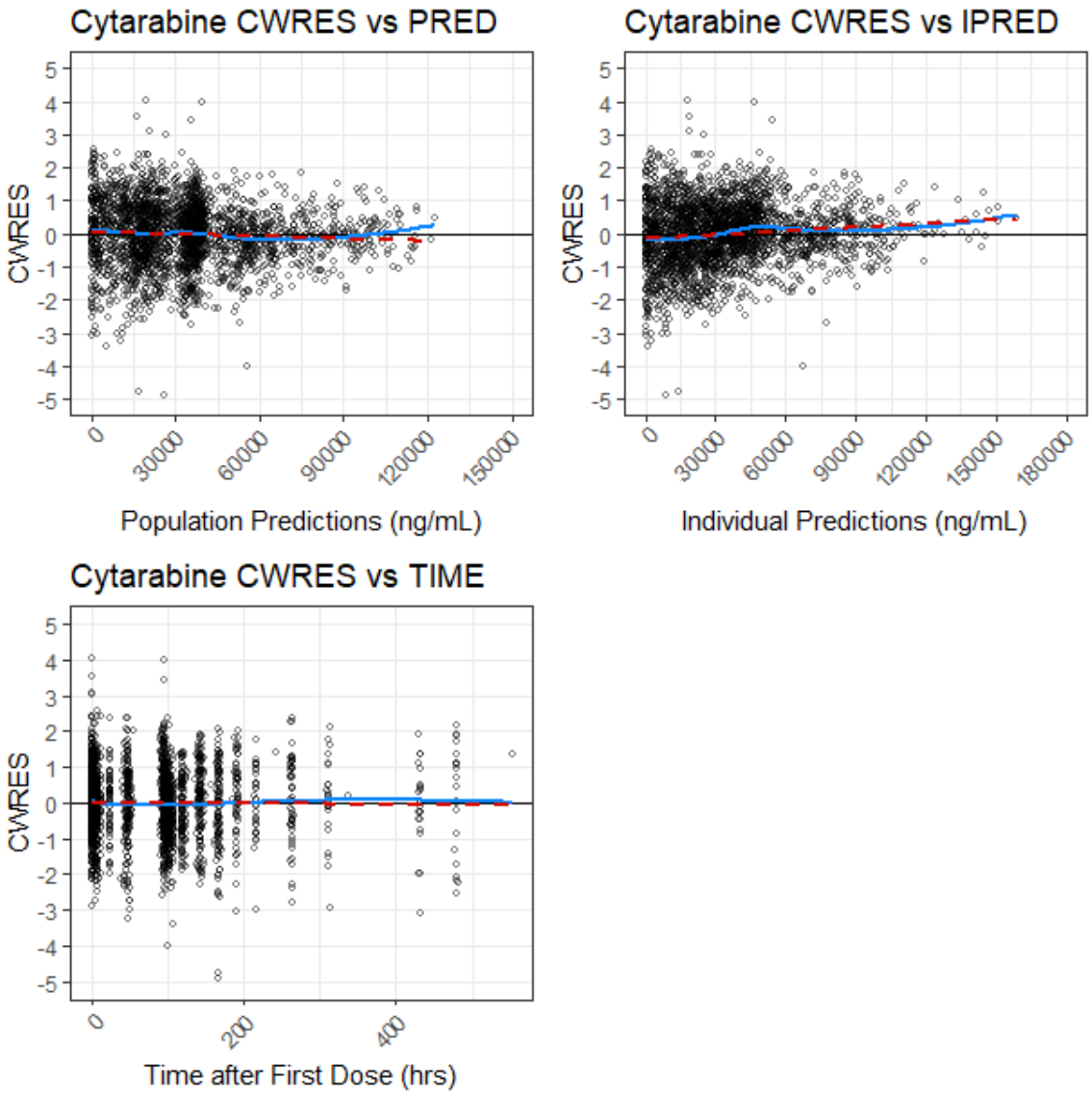
Table 19. Parameter Estimates (RSE) and Median (95% CI) for the Final Cytarabine Model

Fixed-Effects Parameters	Estimate	SE	RSE (%)	Confidence Interval (95%)
tvCL/F	0.101	0.0038	3.762	(0.09355 - 0.1084)
tvVc/F	4.76	0.0934	1.962	(4.577 - 4.943)
tvQ/F	0.00175	0.000587	33.54	(0.0005995 - 0.0029)
tvVp/F	0.133	0.0343	25.79	(0.06577 - 0.2002)
LogErr	0.161	0.00783	4.863	(0.1457 - 0.1763)
BSA_CL	0.940	0.0513	5.457	(0.8395 - 1.041)
BSA_Vc	1.27	0.0473	3.724	(1.177 - 1.363)
BSA_Q	FIXED TO 1	-	-	-
BSA_Vp	FIXED TO 1	-	-	-
BILICL	0.246	0.0603	24.51	(0.1278 - 0.3642)
STUDCL	-0.315	0.0546	-17.33	(-0.422 - -0.208)
STUDVC	-0.197	0.0442	-22.44	(-0.2836 - -0.1104)
Inter-Individual Variability Parameters	Estimate (CV%)	SE	RSE(%)	Shrinkage(%)
Eta(1) (CL)	0.270 (51.96%)	0.0535	19.81	3.1%
Eta(2) (Vc)	0.053 (23.02%)	0.0105	19.81	9.7%
Eta(3) (Q)	FIXED TO ZERO	-	-	-
Eta(4) (Vp)	FIXED TO ZERO	-	-	-
Eta(5) (LogErr)	0.418 (64.65%)	0.0669	16	13.6%
Intra-Individual Variability Parameters	Estimate	SE	RSE(%)	Shrinkage(%)
Sigma(1)	FIXED TO 1	-	-	12.5%

OBJV = -4306.320; Condition = 205.37.
Source: Reviewer Analysis

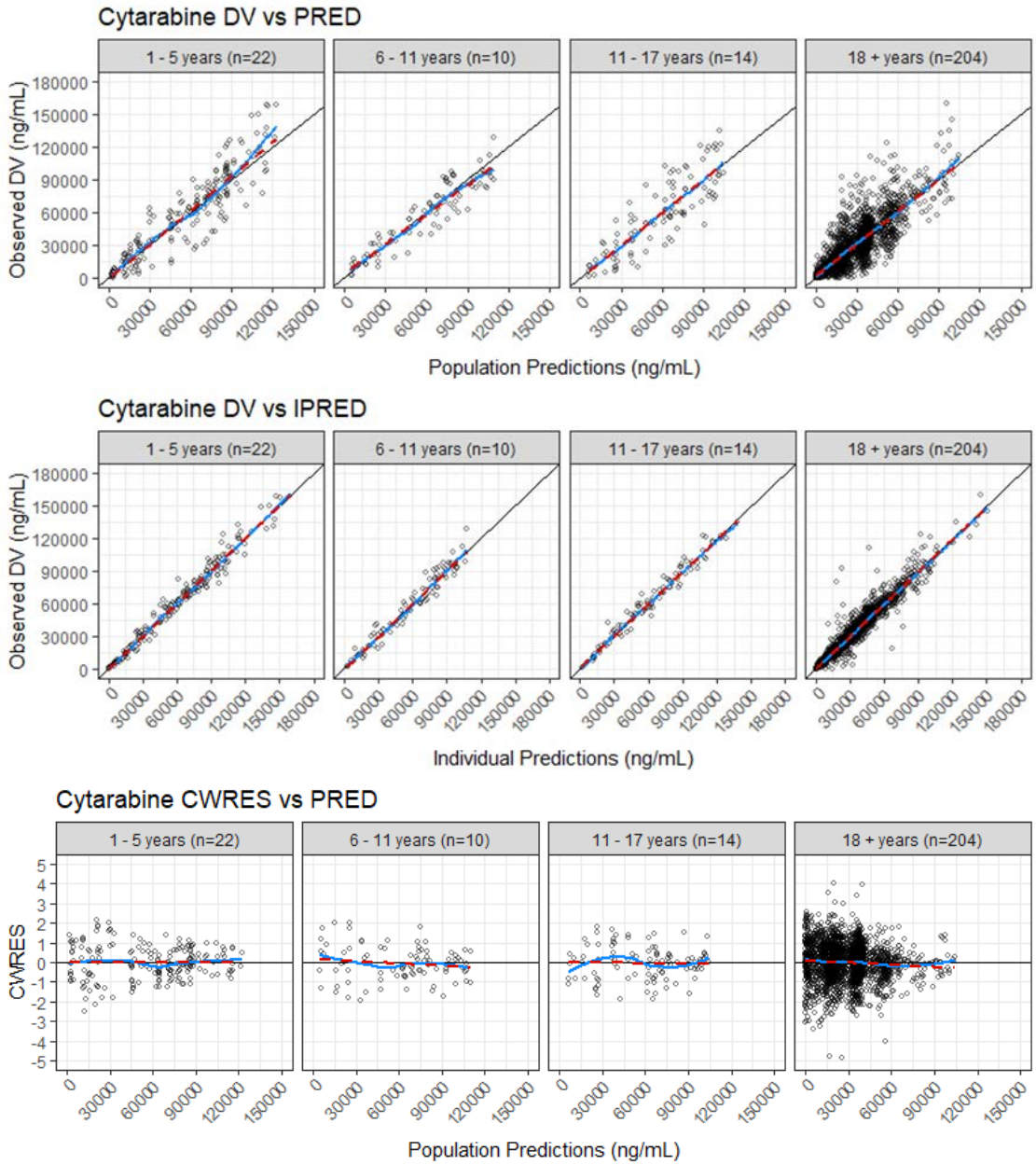
Figure 13. Goodness-of-Fit Plots for Final Cytarabine Model

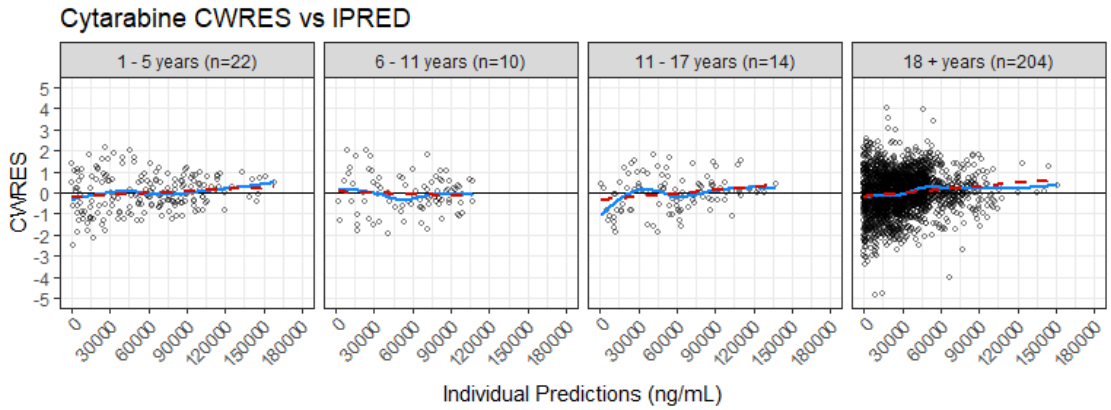




Loess in solid blue; Linear regression in dashed red. Cytarabine LLOQ=5 ng/mL
Source: Reviewer Analysis

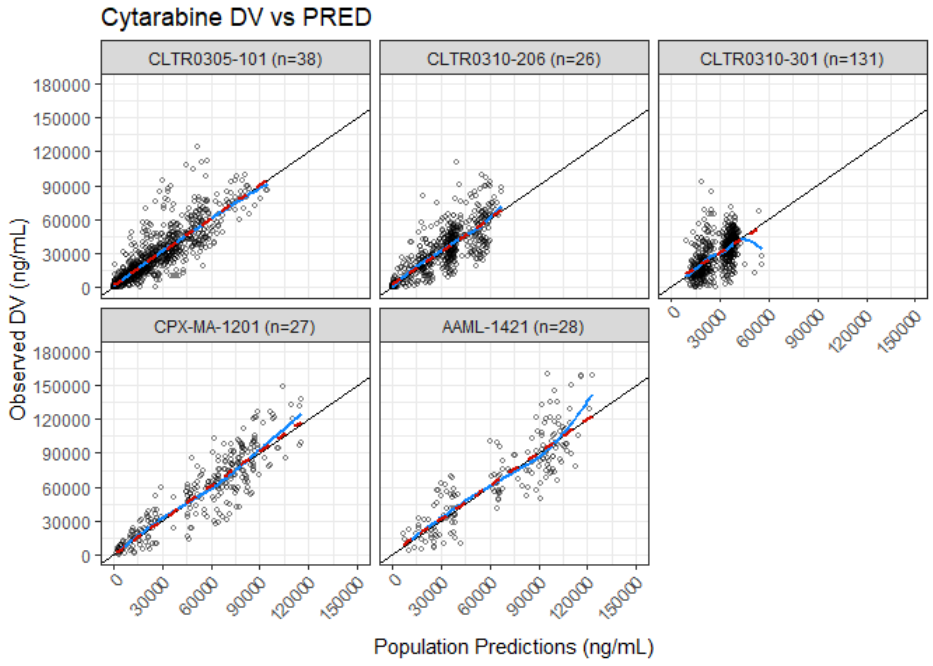
Figure 14. Goodness-of-Fit Plots for Cytarabine According to Age Category

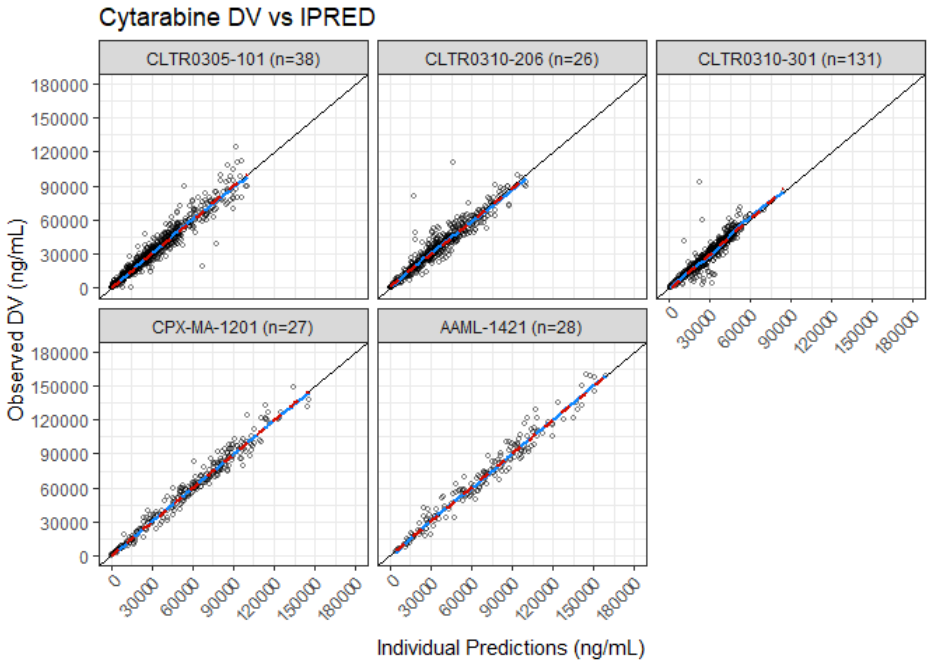


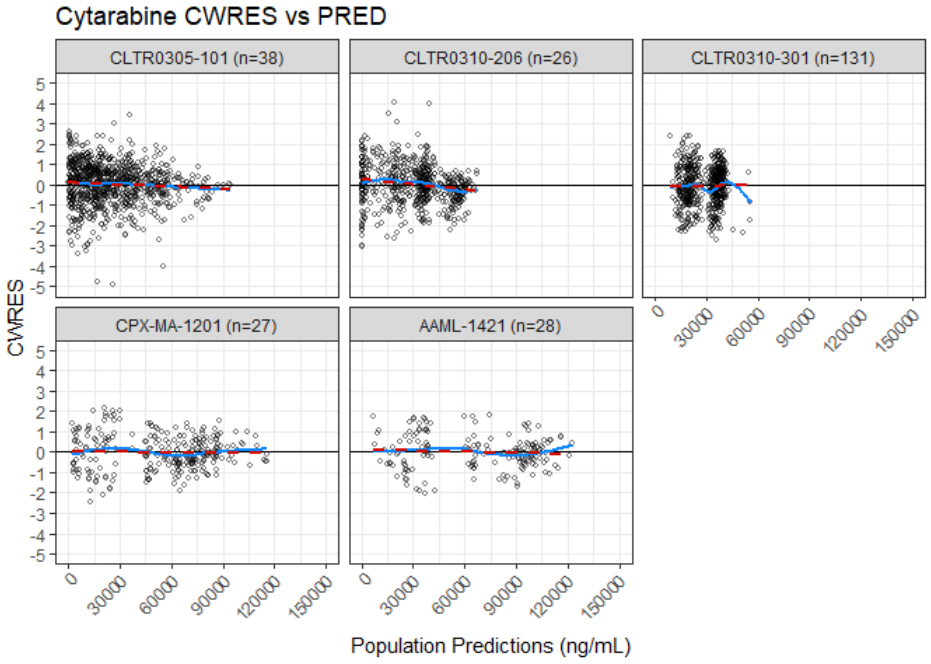


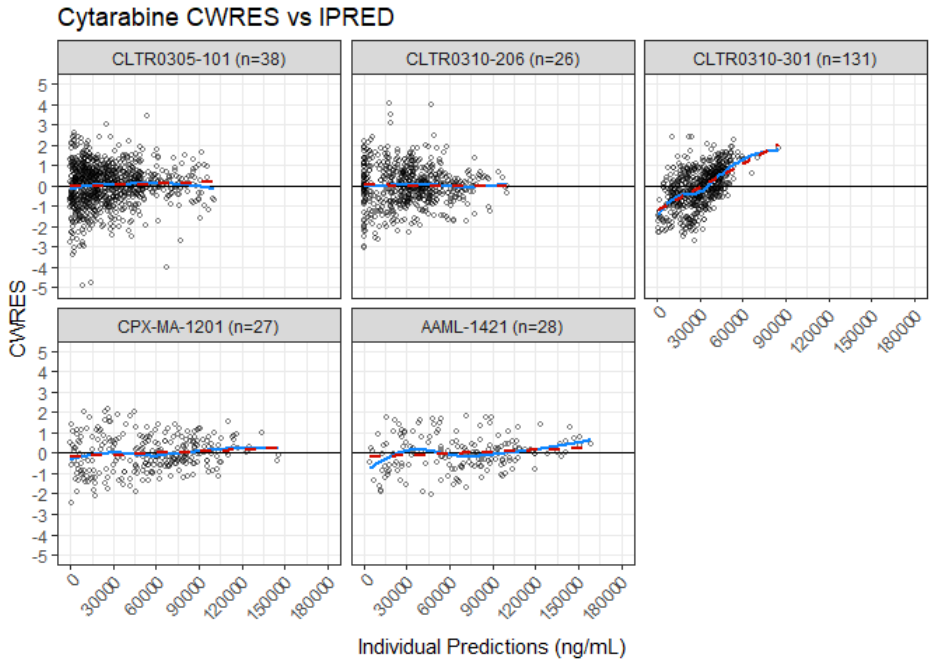
Loess in solid blue; Linear regression in dashed red. Cytarabine LLOQ=5 ng/mL
Source: Reviewer Analysis

Figure 15. Goodness-of-Fit Plots for Cytarabine According to Study




Cytarabine DV vs IPRED
CLTR0305-101 (n=38)
CLTR0310-206 (n=26)
CLTR0310-301 (n=131)
CPX-MA-1201 (n=27)
AAML-1421 (n=28)
Observed DV (ng/mL)
Individual Predictions (ng/mL)


Cytarabine CWRES vs PRED
CLTR0305-101 (n=38)
CLTR0310-206 (n=26)
CLTR0310-301 (n=131)
CPX-MA-1201 (n=27)
AAML-1421 (n=28)
CWRES
Population Predictions (ng/mL)



Loess in solid blue; Linear regression in dashed red. Cytarabine LLOQ=5 ng/mL
Source: Reviewer Analysis

1.3.5 Prediction of Cytarabine PK Parametric using the Final Model

The area-under-the-curve from time 0 to 48 hours after the dose given on Day 5 (AUC48), maximum concentration on Day 5 (Cmax), and concentration 48 hours after the dose given on Day 5 (C48) were calculated using the final cytarabine population PK model. This exposure is summarized by age group in Table 20.

Table 20. Applicant Prediction of Cytarabine PK Exposure Parameters by Age Group

Age Group	Statistic	Day 5 Exposure		
		AUC_{0-48} (µg·h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
1-5 years (135 U/m²)	N	22	22	22
	Arithmetic Mean (CV%)	2767 (33.5%)	102 (28.6%)	29.0 (42.4%)
	SD	928	29.1	12.3
	Geometric Mean (CV%)	2601 (39.3%)	97.6 (30.3%)	25.6 (63.9%)
	Median	2686	98.9	28.9
	Range	940 - 4516	52.2 - 161	4.04 - 51.6
	95% CI	2379 - 3154	89.5 - 114	23.9 - 34.2
6-11 years (135 U/m²)	N	10	10	10
	Arithmetic Mean (CV%)	2783 (17.1%)	93.1 (15.7%)	33.5 (27.5%)
	SD	475	14.6	9.19
	Geometric Mean (CV%)	2740 (19.6%)	92.0 (17.3%)	32.3 (30.3%)
	Median	2856	97.8	32.4
	Range	1701 - 3325	62.5 - 109	17.6 - 47.7
	95% CI	2489 - 3078	84.1 - 102	27.8 - 39.2
12-17 years (135 U/m²)	N	14	14	14
	Arithmetic Mean (CV%)	2806 (34.9%)	94.3 (26.4%)	33.8 (50.2%)
	SD	979	24.9	17.0
	Geometric Mean (CV%)	2644 (37.8%)	91.1 (28.5%)	29.7 (59.2%)
	Median	2610	94.1	31.3
	Range	1309 - 4428	51.1 - 140	11.6 - 65.3
	95% CI	2293 - 3319	81.3 - 107	24.9 - 42.7
Adults (≥18 years) (CLTR0310-206, and CLTR0310-301) (100 U/m²)	N	156	156	156
	Arithmetic Mean (CV%)	1928 (45.9%)	61.3 (31.6%)	25.5 (64.2%)
	SD	884	19.4	16.3
	Geometric Mean (CV%)	1720 (53.6%)	58.3 (32.9%)	19.3 (105.0%)
	Median	1764	59.0	22.0
	Range	410 - 4974	26.2 - 126	0.569 - 84.5
	95% CI	1789 - 2067	58.3 - 64.4	22.9 - 28.0

Source: Table 5, Applicant's Population PK Analysis

Reviewer Comments

Table 20 *states that it contains descriptive statistics of predicted cytarabine PK exposure for pediatric age groups administered 135 units/m^2, but the number of subjects in each age group indicate that both 100 units/m^2 and 135 units/m^2 doses are included in the summaries for pediatric age groups. The PK exposure parameters of AUC48, Cmax, and C48 from Reviewer analysis are summarized in* ***Table 21*** *and presented in Figure 16. Post hoc parameters of CL/F and Vc/F adjusted by BSA effect are presented in Figure 17 for comparison between age groups.*

The individual predicted PK exposure in ***Table 21*** *and Figure 16 show that average AUC48 and Cmax may be slightly higher in pediatric subjects compared to adult subjects following the same units/m^2 dose.*

Figure 17 illustrates that the slightly lower exposure predicted in adults may be related to higher individual estimates of CL/F and Vc/F that cannot be explained by differences in BSA alone.

Differences between the adult and pediatric age groups' exposure appeared larger for the 100 units/m^2 strength compared to 135 units/m^2. This may be related to adult and pediatric/ young adult study differences captured in the Study effects on CL/F and Vc/F that were present in the final cytarabine model. The adult group (18 + years) for 135 units/m^2 included 8 young adults from the pediatric/young adult studies, but the adult group for 100 units/m^2 did not include any subjects from the pediatric/young adult studies. This means that the Study effects which increase exposure were applied to 8 out of 13 adult subjects for 135 units/m^2 and zero out of 169 adult subjects for 100 units/m^2. This could have introduced bias to the summary of adults given 135 units/m^2.

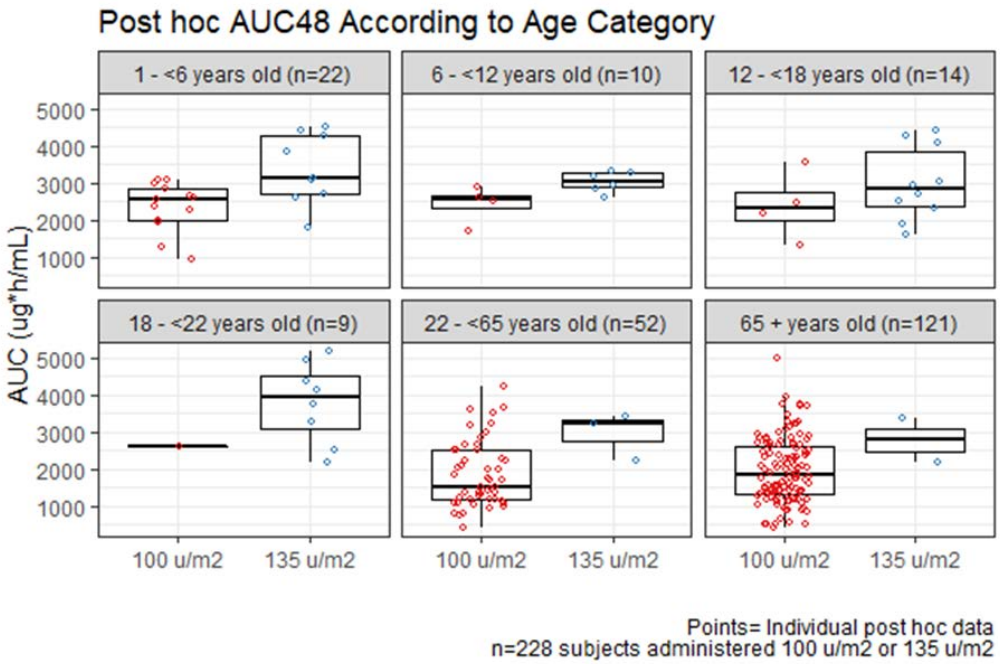
Table 21. Summary of Individual Predicted Cytarabine Exposure from the Final Cytarabine Population PK Model by Age Group for 100 units/m^2 and 135 units/m^2

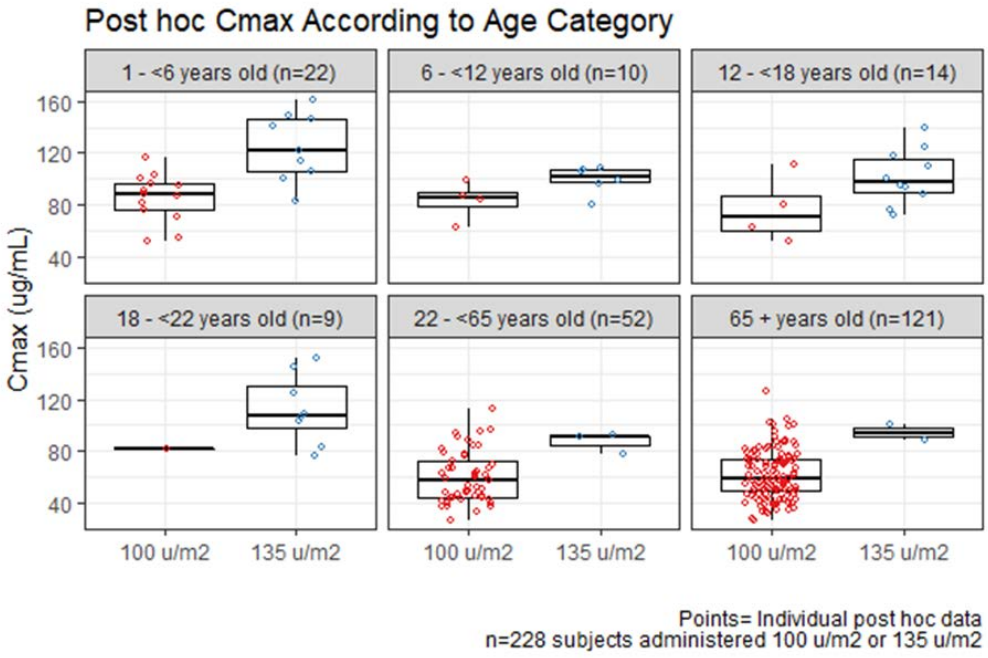
Dose	Parameter	STATISTIC	1 - <6 years old	6 - <12 years old	12 - <18 years old	18 + years old
100 units/m^2	AUC48 (µg x h/mL)	N	13	4	4	169
		Mean (CV%)	2347.4 (28.5%)	2414.3 (20.7%)	2381.7 (39.2%)	1929.6 (45.4%)
		SD	668.9	499.1	932.7	876.2
		GeoMean (GeoCV%)	2230 (36.9%)	2370 (23.1%)	2240 (43.3%)	1730 (52.6%)
		Median	2538	2546.6	2322.4	1762.2
		Minimum - Maximum	940.1 - 3076.5	1701.3 - 2862.7	1309.4 - 3572.6	410.2 - 4974.1
		95% CI	1838.1 - 2711	1895.3 - 2964.8	1492.1 - 3361	1602.2 - 1859.7
100 units/m^2	Cmax (µg/mL)	N	13	4	4	169
		Mean (CV%)	85.6 (21.8%)	83.1 (18.2%)	76.2 (34.3%)	61.3 (31.3%)
		SD	18.7	15.1	26.1	19.2
		GeoMean (GeoCV%)	83.5 (24.3%)	81.9 (19.5%)	73 (34.3%)	58.4 (32.5%)
		Median	88.7	85.6	71.2	59
		Minimum - Maximum	52.2 - 116.4	62.5 - 98.6	51.1 - 111.1	26.2 - 126.5
		95% CI	73.3 - 95.1	67.8 - 99	52.6 - 101.2	55.7 - 61.2
100 units/m^2	C48 (µg/mL)	N	13	4	4	169
		Mean (CV%)	25.1 (40.3%)	27.9 (32.1%)	30.5 (46.8%)	25.5 (63.7%)
		SD	10.1	8.9	14.3	16.2
		GeoMean (GeoCV%)	22 (69.7%)	26.8 (34.2%)	27.4 (62.1%)	19.5 (101.8%)
		Median	28.3	27.4	31.3	22
		Minimum - Maximum	4 - 35.9	17.6 - 39	12.2 - 47.1	0.6 - 84.5
		95% CI	15.6 - 30.9	19.3 - 37.1	15.7 - 48	17.2 - 22.2

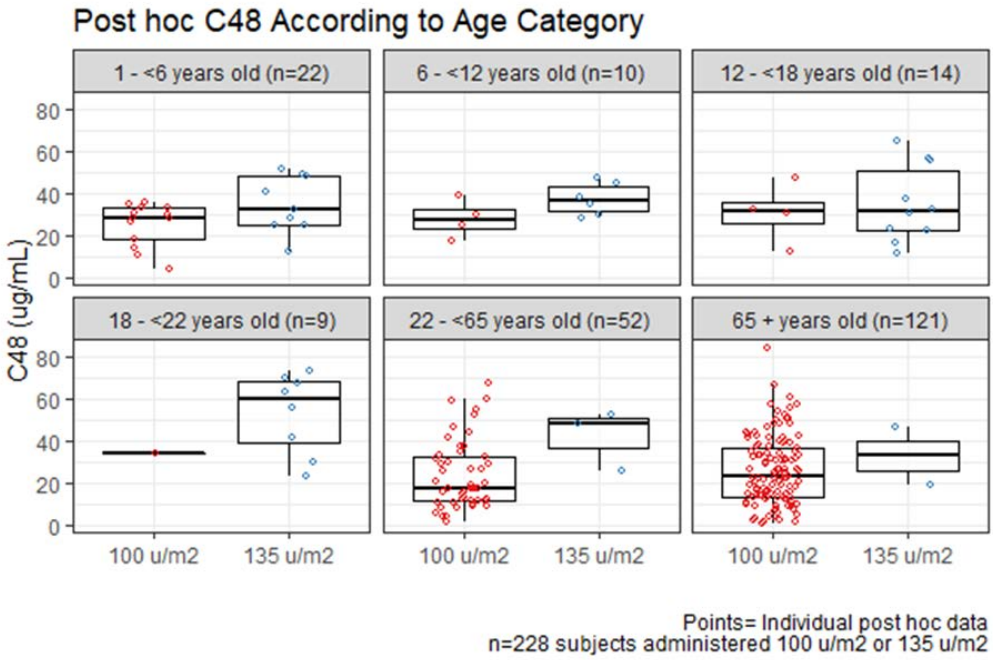
Dose	Parameter	STATISTIC	1 - <6 years old	6 - <12 years old	12 - <18 years old	18 + years old
135 units/m^2	AUC48 (µg x h/mL)	N	9	6	10	13
		Mean (CV%)	3372.3 (28%)	3029.3 (9.1%)	2976.1 (33.3%)	3436.1 (29.6%)
		SD	943.3	275.5	991.5	1016
		GeoMean (GeoCV%)	3240 (31.3%)	3020 (9.3%)	2830 (35.5%)	3300 (30.9%)
		Median	3123.3	3051.4	2827.5	3370.3
		Minimum - Maximum	1792.6 - 4516.4	2618.5 - 3325.4	1593.2 - 4427.5	2156.4 - 5185.4
		95% CI	2656.3 - 3960.5	2803 - 3250.9	2281.7 - 3498.2	2797 - 3885.6
135 units/m^2	Cmax (µg/mL)	N	9	6	10	13
		Mean (CV%)	124.9 (20.9%)	99.8 (10.6%)	101.6 (21.1%)	103.7 (23.3%)
		SD	26.1	10.6	21.5	24.1
		GeoMean (GeoCV%)	122 (22.1%)	99.3 (11.3%)	99.6 (21.5%)	101 (22.2%)
		Median	122.1	102.4	97.8	100.7
		Minimum - Maximum	82.8 - 161.5	80.5 - 109	71.7 - 140	76.8 - 152
		95% CI	106.1 - 141.1	90.8 - 108.7	87.3 - 113.6	90 - 114.2
135 units/m^2	C48 (µg/mL)	N	9	6	10	13
		Mean (CV%)	34.7 (38.9%)	37.2 (21.2%)	35.1 (52.6%)	47.6 (39.2%)
		SD	13.5	7.9	18.5	18.7
		GeoMean (GeoCV%)	32 (48.3%)	36.5 (21.5%)	30.7 (61.5%)	43.7 (47.6%)
		Median	32.3	36.4	31.5	48.6
		Minimum - Maximum	12.4 - 51.6	28.1 - 47.7	11.6 - 65.3	19.2 - 73.9
		95% CI	23.7 - 43.1	30.8 - 43.3	21.6 - 43.6	34.2 - 55.9

AUC48 = area under the concentration-time curve from time 0 to 48h after the dose given on Day 5; Cmax = maximum concentration; C48 = concentration 48 h after the dose given on Day 5. Cytarabine LLOQ=5 ng/mL.
Source: Reviewer Analysis

Figure 16. Individual Predicted Cytarabine Exposure from the Final Cytarabine Population PK Model by Age Group for 100 units/m^2 and 135 units/m^2

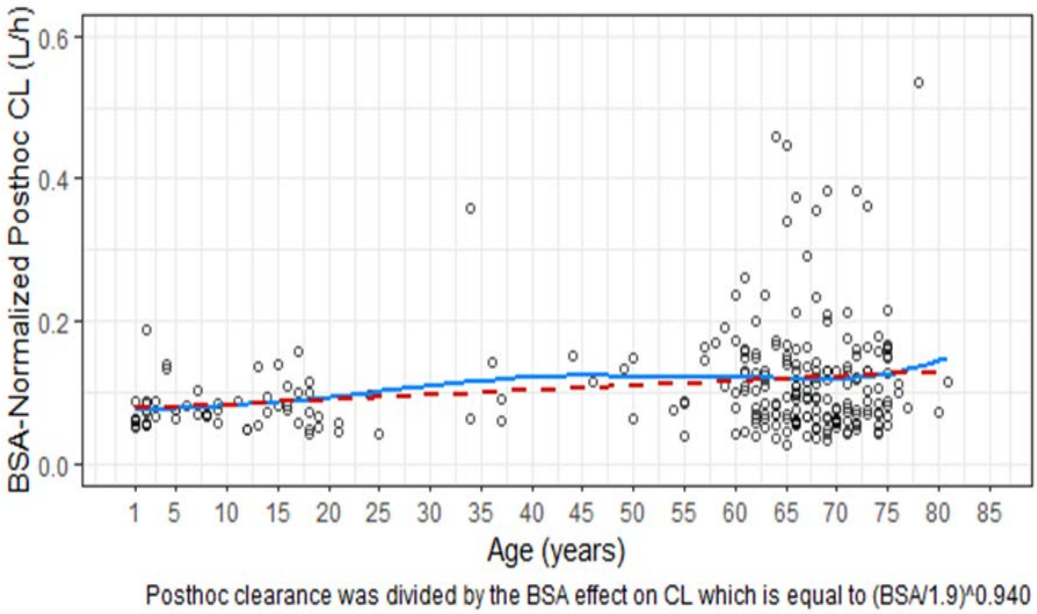


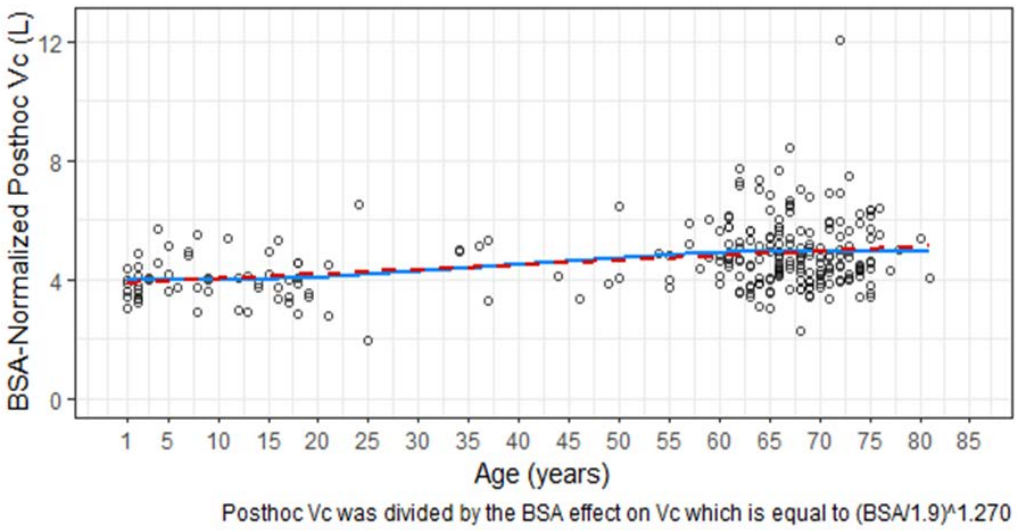




Source: Reviewer Analysis

Figure 17. Post hoc PK Parameters from Final Cytarabine Population PK Model by Age





n=248 total. Loess in solid blue; Linear regression in dashed red. Vc = Central volume of distribution.
Source: Reviewer Analysis

1.3.6 Daunorubicin Base Model

The base model was a two-compartment PK model with first-order elimination from the central compartment. Interindividual variability was applied to the parameters of CL/F, Vc/F, Q/F, and Vp/F. The effect of BSA was included with an estimated allometric exponent on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F). The base model included a bilirubin effect on CL/F, where total bilirubin was centered over 0.6 mg/dL with an estimated allometric exponent. Subjects without a recorded bilirubin were assigned an imputed bilirubin

of 0.6 mg/dL, which effectively negated the bilirubin effect for those subjects. The base model also included estimated effects of formulation which decreased CL/F, Vc/F, Q, and Vp/F for the (b) (4) formulation administered to subjects in Study CLTR0305-101.

1.3.7 Daunorubicin Covariate Analysis

Covariate-versus-ETA plots from the base model output were visually inspected for possible trends to determine which covariates would be investigated for development of the final model. Age (continuous), age group (1- <18 years versus 18+ years), and study (Adult studies CLTR0305-101, CLTR0310-206, and CLTR0310-301 versus pediatric/young adult studies AAML-1421, CPX-MA-1201) were investigated for effects on CL/F in NONMEM. Age group and study were also investigated for effects on Vc/F. Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change.

1.3.8 Daunorubicin Final Model

The base final was a two-compartment PK model with first-order elimination from the central compartment. Interindividual variability was applied to the parameters of CL/F, Vc/F, Q/F, and Vp/F. The effect of BSA centered over 1.9 m^2 was included with an estimated allometric exponent on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F). The final model also included a bilirubin effect on CL/F, where total bilirubin was centered over 0.6 mg/dL with an estimated allometric exponent. Because the same cytarabine dataset was used to develop the base and final models, bilirubin was still imputed as 0.6 mg/dL for all subjects without recorded bilirubin and thus bilirubin only affected adult subjects. The final model also included estimated effects of formulation which decreased CL/F, Vc/F, Q, and Vp/F for the (b) (4) formulation administered to subjects in Study CLTR0305-101.

The only difference in the structure of the final daunorubicin model compared to the base model was the addition of a Study effect which decreased CL/F by 33.4% and decreased Vc/F by 18.9% for subjects in Studies CPX-MA-1201 and AAML-1421.

The Applicant's parameter estimates for the final covariate model are listed in Table 22. The prediction-corrected Visual Predictive Check (pcVPC) plot for the final covariate model with all data is shown in Figure 18.

Table 22. Applicant Daunorubicin Final Population PK Model – Parameter Estimates

Parameter	Units	Estimate	SE	RSE%	95% CI	Shrinkage	Equation
OFV		-4433.8649					
CL	L/h	0.140	0.00559	4.0%	0.129 - 0.151		CL = tvCL · exp(ηCL)
BSA_CL		0.876	0.103	11.7%	0.675 - 1.08		× (BSA/1.9)$^{BSA\_CL}$
Bili_CL		0.155	0.0513	33.0%	0.0548 - 0.256		× (Bilirubin/0.6)$^{Bili\_CL}$ if bilirubin is available*
Form_CL		-0.199	0.0829	41.7%	-0.361 - -0.0364		× exp(Form_CL) if (b) (4) Formulation
Stud_CL		-0.406	0.0901	22.2%	-0.583 - -0.23		× exp(Stud_CL) if Study 1201 or 1421
Vc	L	4.04	0.0845	2.1%	3.88 - 4.21		Vc = tvVc · exp(ηVc)
BSA_Vc		1.23	0.0584	4.7%	1.12 - 1.35		× (BSA/1.9)$^{BSA\_Vc}$
Form_Vc		-0.167	0.0388	23.2%	-0.243 - -0.0912		× exp(Form_Vc) if (b) (4) Formulation
Stud_Vc		-0.209	0.0508	24.3%	-0.308 - -0.109		× exp(Stud_Vc) if Study 1201 or 1421
Q	L/h	0.0375	0.00843	22.5%	0.0210 - 0.0540		Q = tvQ · exp(ηQ)
BSA_Q		1.00	fixed				× (BSA/1.9)$^{BSA\_Q}$
Form_Q		-1.21	0.586	48.3%	-2.36 - -0.0650		× exp(Form_Q) if (b) (4) Formulation
Vp	L	0.788	0.173	22.0%	0.449 - 1.13		Vp = tvVp · exp(ηVp)
BSA_Vp		1.00	fixed	-	-		× (BSA/1.9)$^{BSA\_Vp}$
Form_Vp		-1.49	0.376	25.2%	-2.23 - -0.756		× exp(Form_Vp) if (b) (4) Formulation
LogErr		0.141	0.00799	5.7%	0.125 - 0.157	13.2%	ln(Cobs) = ln(Cpred) + LogErr · exp(ηLogErr)
BSV_CL		0.200(47.1%)	0.0208	10.4%	0.159 - 0.241	3.2%	ω^2CL
BSV_Vc		0.0372(19.5%)	0.00440	11.8%	0.0286 - 0.0458	10.3%	ω^2Vc
BSV_Q		1.80(224.7%)	0.298	16.5%	1.22 - 2.38	30.2%	ω^2Q
BSV_Vp		1.62(201.8%)	0.367	22.6%	0.903 - 2.34	28.8%	ω^2Vp
BSV_LogErr		0.392(69.3%)	0.0501	12.8%	0.294 - 0.491	17.9%	ω^2LogErr

CL = clearance, BSA_CL; BSA effect on CL; Form_CL = formulation effect (b) (4) on CL; Stud_CL = study effect on CL

Vc = central volume of distribution; BSA_Vc = BSA effect on Vc; Form_Vc = formulation effect (b) (4) on Vc; Stud_Vc = study effect on Vc

Q = peripheral clearance; BSA_Q = BSA effect on Q; Form_Q = formulation effect (b) (4) on Q

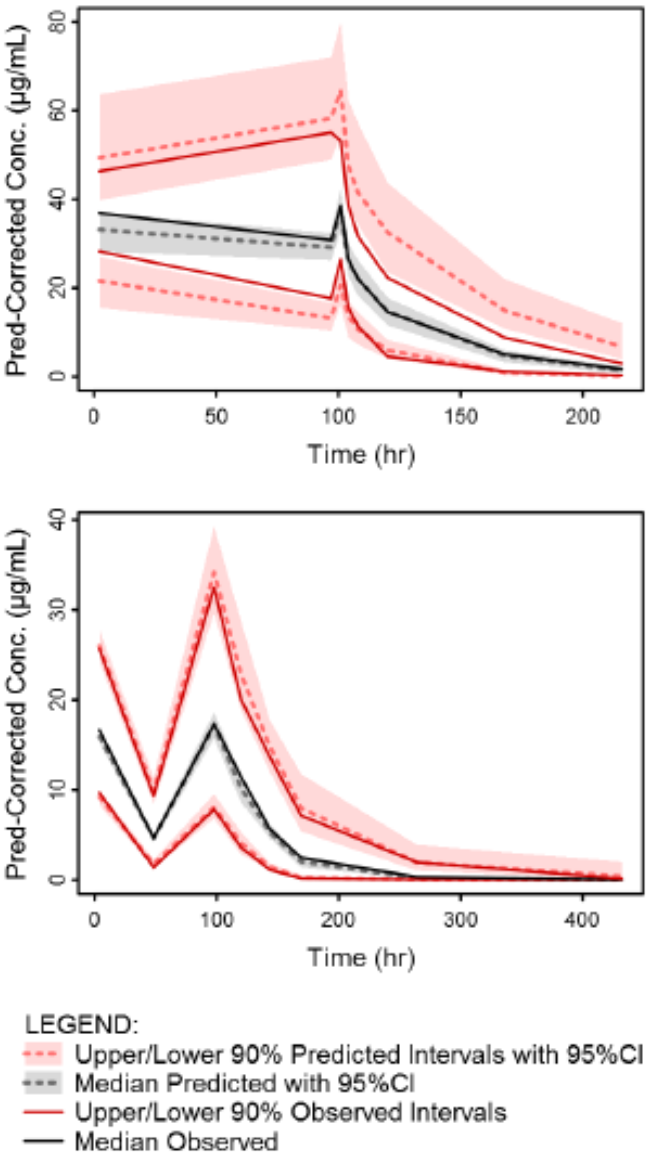
Vp = peripheral volume of distribution; BSA_Vp = BSA effect on Vp; Form_Vp = formulation effect (b) (4) on Vp

OFV = objective function value; BSV = between-subjects variability, CI = confidence intervals, RSE = relative standard error, SE = standard error.

NOTE: BSV% were calculated as $(\exp(\omega^2)-1)^{0.5}$

Source: Table 13-25, Applicant's Population PK Analysis

Figure 18. Goodness-of-Fit for Final Model of Daunorubicin: Population and Individual Predicted vs. Observed Concentrations in Children and Young Adults (Top) and Adults (Bottom)



Source: Figure 6, Applicant's Population PK Analysis

Reviewer Comments

However, Table 22 reports final estimates and standard error from only the first subroutine (SAEM) although the reported OFV is from the final subroutine (SAEM then IMP+I). Final parameter estimates are similar between the SAEM and the SAEM-then-IMP+I estimation methods, but multiple values of SE (and related RSE and 95% CI) are significantly different.

Table 23 *contains parameter estimates for the final daunorubicin model complete estimation (SAEM then IMP+I) from Reviewer analysis.*

Table 23. Parameter Estimates (RSE) and Median (95% CI) for the Final Daunorubicin Model

Fixed-Effects Parameters	Estimate	SE	RSE (%)	Confidence Interval (95%)
tvCL/F	0.138	0.008	5.797	(0.1223 - 0.1537)
tvVc/F	4.01	0.207	5.162	(3.604 - 4.416)
tvQ/F	0.0345	0.0139	40.29	(0.007257 - 0.06174)
tvVp/F	0.757	0.202	26.68	(0.3611 - 1.153)
LogErr	0.144	0.0121	8.403	(0.1203 - 0.1677)
BSA_CL	0.926	0.0408	4.406	(0.846 - 1.006)
BSA_Vc	1.21	0.182	15.04	(0.8533 - 1.567)
BSA_Q	1	0	0	(1 - 1)
BSA_Vp	1	0	0	(1 - 1)
FORM_CL	-0.16	0.24	-150	(-0.6304 - 0.3104)
FORM_Vc	-0.151	0.229	-151.7	(-0.5998 - 0.2978)
FORM_Q	-0.653	2.86	-438	(-6.258 - 4.952)
FORM_Vp	-1.1	1.76	-160	(-4.55 - 2.35)
BILICL	0.148	0.0959	64.8	(-0.03996 - 0.336)
STUDCL	-0.346	0.0892	-25.78	(-0.5208 - -0.1712)
STUDVC	-0.191	0.0556	-29.11	(-0.3 - -0.08203)
Inter-Individual Variability Parameters	**Estimate (CV%)**	**SE**	**RSE(%)**	**Shrinkage(%)**
Eta(1) (CL)	0.198 (44.5%)	0.0247	12.47	2.88%
Eta(2) (Vc)	0.037 (19.24%)	0.0103	27.84	10.53%
Eta(3) (Q)	1.88 (137.1%)	0.404	21.49	29.10%
Eta(4) (Vp)	1.51 (122.9%)	0.58	38.41	29.03%
Eta(5) (LogErr)	0.39 (62.45%)	0.0685	17.56	17.98%
Intra-Individual Variability Parameters (sigma^2)	**Estimate**	**SE**	**RSE(%)**	**Shrinkage(%)**
Sigma(1)	1	0	0	14.09%

OBJV = -4434.943; Condition = 7680.41.
Source: Reviewer Analysis

The RSE is 150% or greater for the fixed-effects parameters of formulation effects on CL, Vc, Q, and Vp (FORM_CL, FORM_Vc, FORM_Q, and FORM_Vp). Additionally, these four parameters all have 95% CIs that include zero where the formulation has no effect on daunorubicin PK. In the

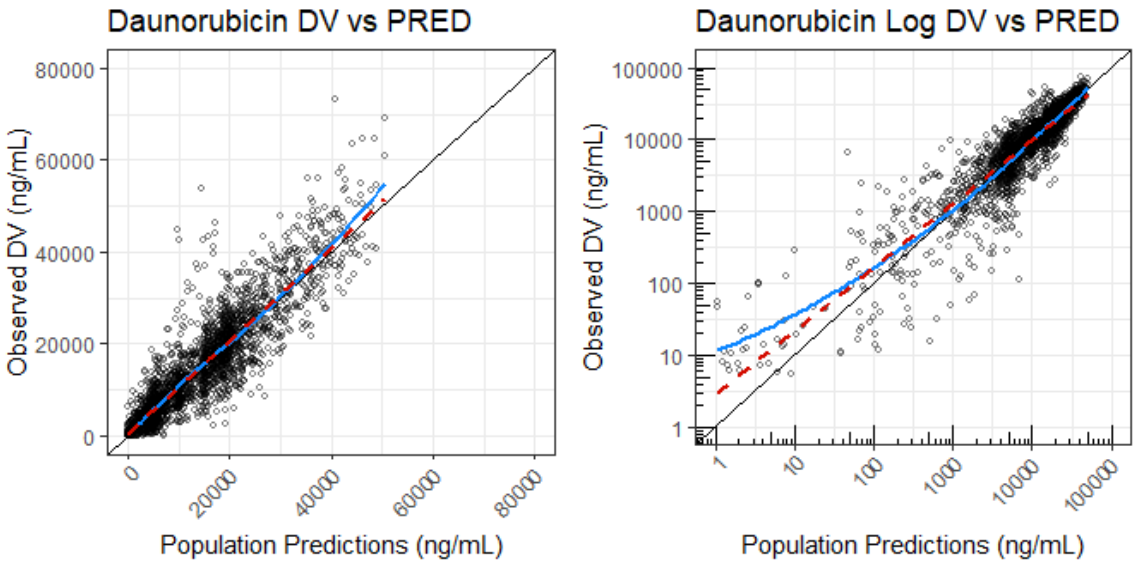
population PK dataset, only Study CLTR0310-305 (n=38) administered the (b) (4) *formulation while all other studies administered the lyophilized formulation. This may contribute to high variability and/or uncertainty for parameters based on formulation.*

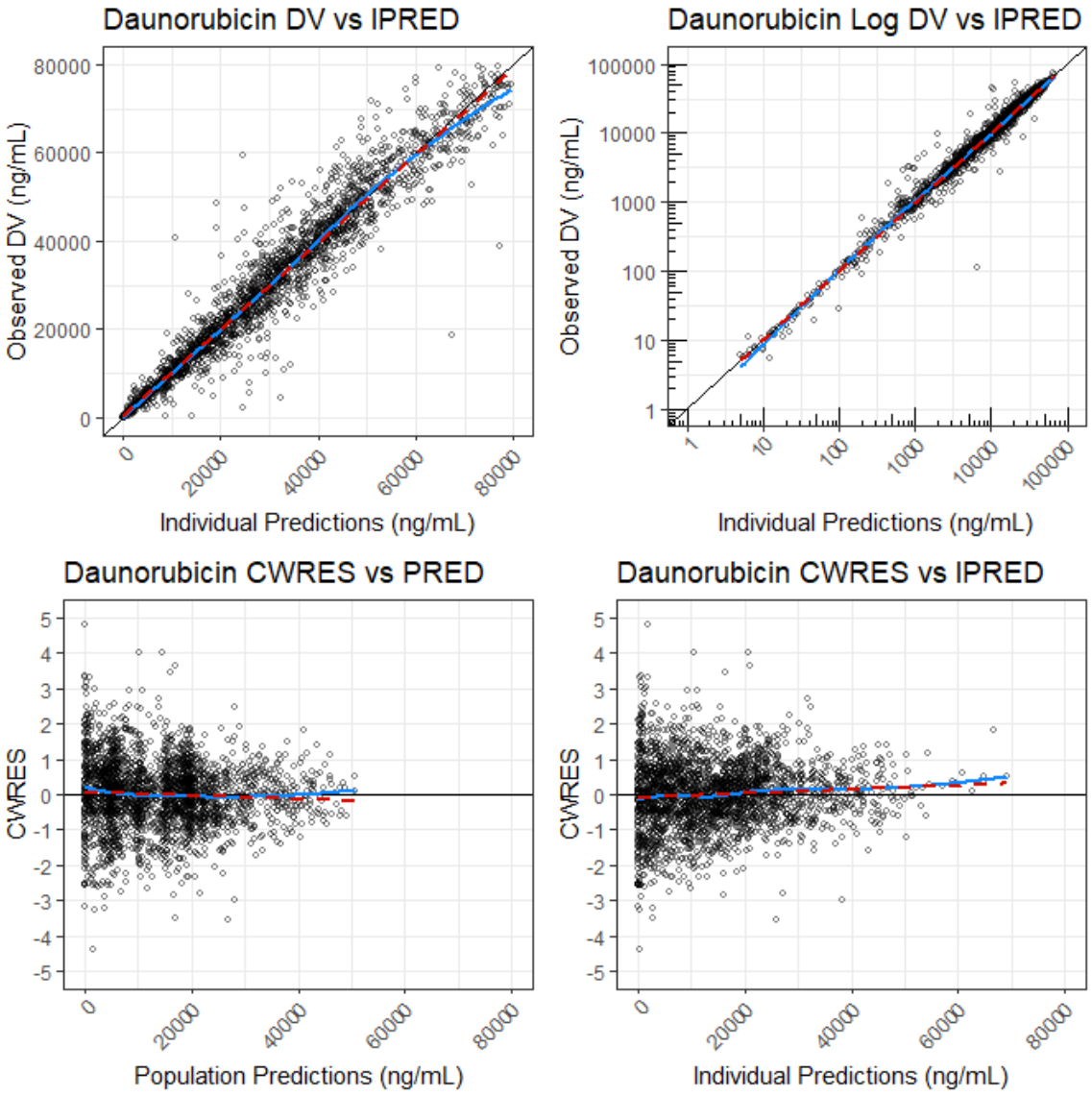
Final estimations for the BSA_CL exponent and the BSA_Vc exponent both have 95% CIs that include 1.0 where the exponent does not affect the parameter (95% CI of 0.846 to 1.006 for BSA_CL and 0.8533 to 1.567 for BSA_Vc in Reviewer Analysis). The bilirubin effect on clearance also has a 95% CI that include zero where the bilirubin has no effect on cytarabine PK (-0.03996 to 0.336). The condition number of 7680.4 is also high, further indicating that the model may be over-parameterized. Inclusion of these parameters may not be necessary.

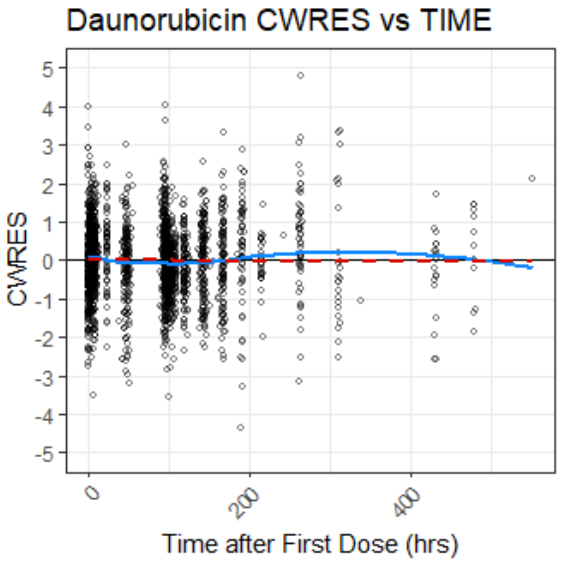
The goodness-of-fit plots for the final model for all data are shown in ***Figure 19****. Key goodness-of-fit plots grouped by age category are shown in* ***Figure 20****. Key goodness-of-fit plots grouped by study number are shown in* ***Figure 21****.*

The goodness-of-fit plots indicate acceptable characterization of daunorubicin PK in adults and pediatric subjects down to 1 year of age, although the model may be overparameterized and may benefit from removal of some estimated parameters.

Figure 19. Goodness-of-fit Plots for Final Daunorubicin Model

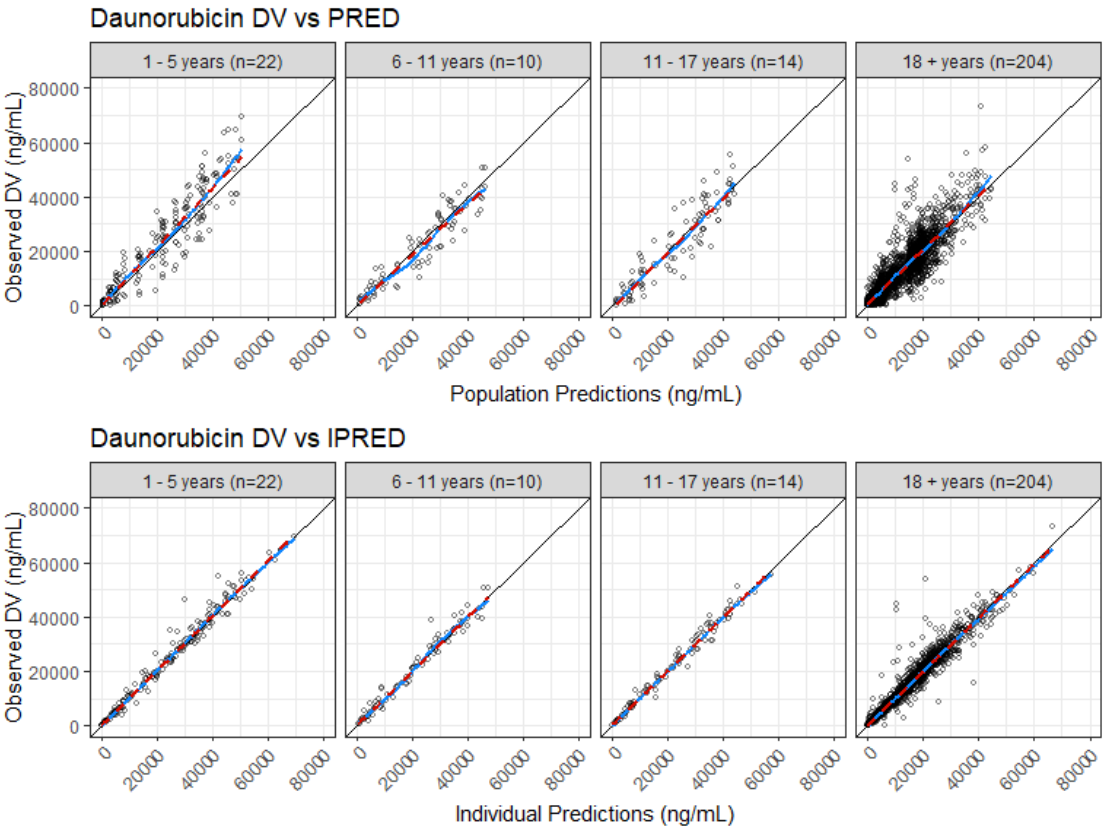



Daunorubicin DV vs IPRED
Observed DV (ng/mL)
Individual Predictions (ng/mL)
Daunorubicin Log DV vs IPRED
Observed DV (ng/mL)
Individual Predictions (ng/mL)
Daunorubicin CWRES vs PRED
CWRES
Population Predictions (ng/mL)
Daunorubicin CWRES vs IPRED
CWRES
Individual Predictions (ng/mL)



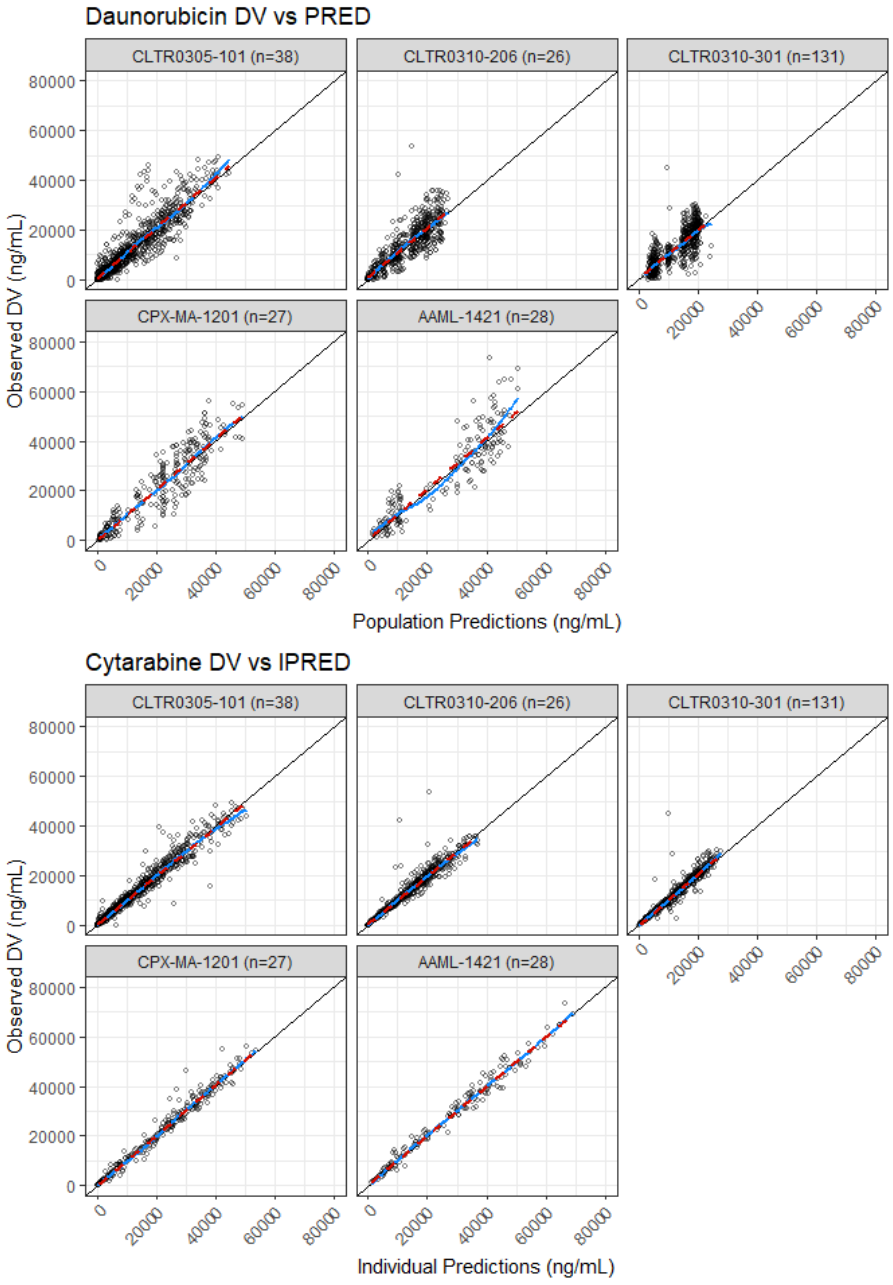
Loess in solid blue; Linear regression in dashed red. Daunorubicin LLOQ= 5 ng/mL.
Source: Reviewer Analysis

Figure 20. Goodness-of-Fit Plots for Daunorubicin According to Age Category



Loess in solid blue; Linear regression in dashed red. Daunorubicin LLOQ= 5 ng/mL.
Source: Reviewer Analysis

Figure 21. Goodness-of-Fit Plots for Daunorubicin According to Study



Loess in solid blue; Linear regression in dashed red. Daunorubicin LLOQ= 5 ng/mL.
Source: Reviewer Analysis

1.4 Reviewer's Independent Analysis

1.4.1 Introduction

The reviewer conducted additional sensitivity analyses based on the Applicant's final cytarabine model in order to verify the model and covariate evaluation.

1.4.2 Methods

Dataset handling and generation of diagnostics and other plots was conducted using R version 4.0.2. NONMEM version 7.3 was used for population PK analysis. The PK dataset were provided by the Applicant and submitted to NONMEM without edit. Additional models were developed by editing the final population PK model control file provided by the Applicant.

1.4.3 Results

Additional cytarabine population PK models were tested using the Applicant's final model as a reference. Key models in the analyses are summarized in **Table 24**. Any changes from the reference model structure are in the model description. The goodness-of-fit plots were similar to the reference model unless specified in the comments.

Table 24. Summary of Reviewer's Sensitivity Analysis for Cytarabine

Run	Model description	Condition number	OFV	dOFV	Comments
001	Reference model (SAEM then IMP+I estimation)	205.4	-4306.32	-	-
002	BSACL exponent fixed to 1.0	42.3	-4306.22	0.1	STUDCL slightly closer to zero (from 27.0% decrease to 24% decrease in pediatric CL); RSE on STUDCL decreased slightly from 17.3% to 12.6%
003	Same structure as reference; IMP+I estimation method (without SAEM)	204	-4306.32	0.0	This model structure was relatively simple and SAEM subroutine likely would not add much benefit, so the remainder of the independent analysis used IMP+I by itself.
005	Removed STUDCL effect	63.7	-4299.03	7.3	BSACL 95% CI was 1.112-1.1228 (reference model BSACL 95% CI was 0.839-1.041 which included 1.0)
006	Removed STUDVC effect	168.1	-4292.29	14.0	No significant changes besides increased OFV
007	Removed STUDCL and STUCVC effects	37.1	-4285.36	21.0	BSACL 95% CI was 1.114-1.226 (reference model BSACL 95% CI was 0.839-1.041 which included 1.0)
008	Removed BILIRUBIN effect on CL	204.7	-4295.75	10.6	Note: only adult studies had total bilirubin measurements and so only adults had CL affected by bilirubin
009	Added age effect (exp) on CL	1778.3	-4302.15	4.2	Did not optimize after 1000 iterations; At final iteration, all parameter estimates were similar to reference model except STUDCL

Run	Model description	Condition number	OFV	dOFV	Comments
					(likely confounding the age effect and vice versa); DV vs PRED fit slightly worse than reference
010	Added categorical age effect (prop shift) on CL for >=60yo	129.1	-4305.44	0.9	AGECL reduced CL by 15.9% when AGE>=60; STUDCL magnitude increased (from 27.0% decrease to 36.9% decrease in pediatric CL); RSE% on CL increased from 3.8% to 8.6%; RSE% on BSACL increased from 5.5% to 11.9%; RSE% on STUDCL increased from 17.3% to 22.6%; RSE% on AGECL effect was relatively high at 48.9%
011	Added categorical age effect (prop shift) on CL for <18yo	302.8	-4309.26	-2.9	AGECL increased CL by 36.2% when AGE<18; STUDCL magnitude increased (from 27.0% decrease to 42.3% decrease in pediatric CL); RSE% on BILICL decreased from 24.5% to 14.4%; RSE% on STUDCL decreased from 17.3% to 10.9%; RSE% on STUDVC increased from 22.4% to 34.2%
012	Added categorical age effect (prop shift) on CL for <18yo; Removed STUDCL effect	137.0	-4300.72	5.6	AGECL decreased CL by 18.2% when AGE<18
013	Two separate ETA terms for pediatric/young adult studies and for adult studies	14452.9	-4321.52	-15.2	BSACL 95% CI included 1.0 (0.48 – 1.42); BILICL 95% CI included both 1.0 and zero (-0.74 – 1.3); STUDCL 95% CI included zero (-0.94 – 0.32) ETA(CL) in reference model had CV% 52.0%; ETA(CL) for adult studies increased to CV% 57.1% while ETA(CL) for pediatric/young adult studies decreased to 33.3%; Shrinkage on pediatric/young adult ETA(CL) was 53.5%; RSE% on BSACL increased from 5.5% to 25.3%; RSE% on BILICL increased from 24.5% to 191.4%; RSE% on STUDCL increased from 17.3% to 103.9%; RSE% on STUDVC increased from 22.4% to 46.4%
014	Two separate ETA terms for pediatric/young adult studies and for adult studies; Fixed BSACL exponent to 1.0; Removed BILICL effect and STUDCL	37.25	-4287.07	19.25	ETA(CL) in reference model had CV% 52.0%; ETA(CL) for adult studies increased to CV% 58.5% while ETA(CL) for pediatric/young adult studies decreased to 42.4%; Shrinkage on pediatric/young adult ETA(CL) was 54.7%

Source: Reviewer Analysis

Run 003 utilized the same model structure but omitted the SAEM estimation subroutine that occurred before IMP+I estimation in the reference model. The model was relatively simple enough that this did not appear to result in any differences in model output. Subsequent independent review model runs utilized the IMP+I estimation method without the SAEM subroutine.

Adding categorical or continuous age effects to the model demonstrated that the age covariate and Study covariate (pediatric/young adult versus adult) are interrelated in the population PK dataset. Addition of an age effect on CL resulted in significant changes to the final estimate of the STUDCL parameter to compensate. The STUDCL effect appeared to be more beneficial when included in the model compared to various AGECL effects, and so it seems that the Study covariate captures some factor(s) that are not entirely a result of age. Upon request, the Applicant explained that the identified "Study effect" was thought to be due to an assay effect and not due to changes associated with age, study protocol(s), or other factors. However, an assay effect was not evident based on the submitted bioanalytical reports.

Overall, the Applicant's final cytarabine population model is acceptable, although it should be noted that the Study effects' contributing factors are not well characterized and it is uncertain if this effect is intrinsic or extrinsic and whether it should be included for simulation of exposure in different patient populations.

2. Monte Carlo Simulation of Exposure

2.1 Monte Carlo Simulation Summary

Cytarabine exposure was simulated in virtual populations using the final cytarabine population PK model with 100 units/m^2 and 135 units/m^2. Predicted exposure for a given dosing strength is not expected to significantly differ according to age group in subjects down to 1 year of age.

2.2 Applicant's Monte Carlo Simulation Analysis

The Applicant's primary objectives detailed in the report entitled "Monte Carlo Simulations to Support Dosing of CPX-351 in Pediatric Patients with Newly Diagnosed Therapy-related Acute Myeloid Leukemia (t-AML) or AML with Myelodysplasia-related Changes (AML-MRC)" were to:

- Predict PK exposure levels of cytarabine in a virtual population of pediatric patients (1 to 17 years old) with newly diagnosed t-AML or AML-MRC after intravenous administration of 100 and 135 units/m^2 of CPX-351 over 90 minutes on Days 1, 3, and 5 in Cycle 1.
- Compare model-predicted exposure levels of cytarabine in pediatric patients to those observed in adult patients.

2.2.1 Virtual Patient Populations for Simulation

A virtual population was generated containing 1000 virtual subjects who were 1 - <6 years old, 1000 virtual subjects who were 6 - <12 years old, 1000 virtual subjects who were 12 - <18 years old, and 1000 virtual adults (18 years and older) re-sampled with replacement from the

cytarabine population PK dataset. Virtual pediatric subjects and virtual adult subjects were included in a dataset for simulation with two strengths of CPX-351: 100 and 135 units/m^2 over 90 minutes on Days 1, 3, and 5 in Cycle 1. All virtual subjects, including virtual adults, were assigned a total bilirubin value of 0.6 mg/dL.

2.2.2 Population PK Model-Predicted Exposure in Virtual Patient Populations

The final cytarabine population PK model was used to predict cytarabine exposure (Cmax, AUC48, and C48) in the 4000 virtual subjects with two strengths of CPX-351: 100 and 135 units/m^2 over 90 minutes on Days 1, 3, and 5 in Cycle 1. Bilirubin was assumed to be equal to 0.6 mg/dL in all virtual subjects regardless of age, which meant that bilirubin had no effect on clearance of virtual subjects. The Study effect on CL/F and the Study effect on Vc/F were applied to all virtual subjects regardless of age.

A summary of model-predicted exposure according to dose and age groups is listed in Table 25.

Table 25. Applicant's Descriptive Statistics of Exposure Parameters of Cytarabine in Virtual Pediatric Patients with Newly Diagnosed t-AML or AML-MRC for the 100 and 135 units/m^2 Doses

Dose (units/m^2)	Parameter	Geometric Mean (Geometric CV%) Arithmetic Mean (CV%) Median [5th – 95th Percentiles]			
		1 -<6 years (n=1000)	6 - <12 years (n=1000)	12 - <18 years (n=1000)	Adults (n=1000)
100	AUC_{48} (µg.h/mL)	2483 (42.8%) 2258 (47.2%) 2296.05 [1051 - 4484]	2507 (39.8%) 2310 (43.4%) 2354.68 [1104 - 4277]	2459 (39.1%) 2267 (43.5%) 2353.07 [1086 - 4219]	2469 (38.6%) 2287 (41.9%) 2384.32 [1075 - 4193]
	C_{max} (µg/mL)	89.1 (24.1%) 86.6 (24.3%) 86.52 [58.7 - 129]	83.9 (24.4%) 81.5 (24.4%) 81.29 [55.0 - 120]	78.1 (24.4%) 75.8 (24.7%) 76.29 [50.9 - 111]	77.2 (25.2%) 74.9 (24.9%) 74.37 [51.4 - 113]
	C_{48} (µg/mL)	25.4 (66.1%) 18.9 (114.5%) 22.29 [3.43 - 57.0]	27.5 (57.7%) 21.8 (97.7%) 25.42 [5.00 - 56.3]	28.2 (54.6%) 23.0 (83.5%) 26.84 [6.03 - 56.0]	28.7 (52.6%) 23.8 (79.1%) 27.78 [6.21 - 55.3]
135	AUC_{48} (µg.h/mL)	3352 (42.8%) 3048 (47.2%) 3099.67 [1419 - 6053]	3385 (39.8%) 3119 (43.4%) 3178.82 [1490 - 5774]	3320 (39.1%) 3060 (43.5%) 3176.64 [1465 - 5695]	3333 (38.6%) 3087 (41.9%) 3218.83 [1452 - 5661]
	C_{max} (µg/mL)	120 (24.1%) 117 (24.3%) 116.8 [79.3 - 174]	113 (24.4%) 110 (24.4%) 109.74 [74.2 - 162]	105 (24.4%) 102 (24.7%) 102.99 [68.7 - 150]	104 (25.2%) 101 (24.9%) 100.4 [69.4 - 153]
	C_{48} (µg/mL)	34.3 (66.1%) 25.5(114.5%) 30.09 [4.64 - 76.9]	37.1 (57.7%) 29.4 (97.7%) 34.31 [6.75 - 76.0]	38.0 (54.6%) 31.1 (83.5%) 36.24 [8.13 - 75.6]	38.7 (52.6%) 32.2 (79.1%) 37.5 [8.38 - 74.6]

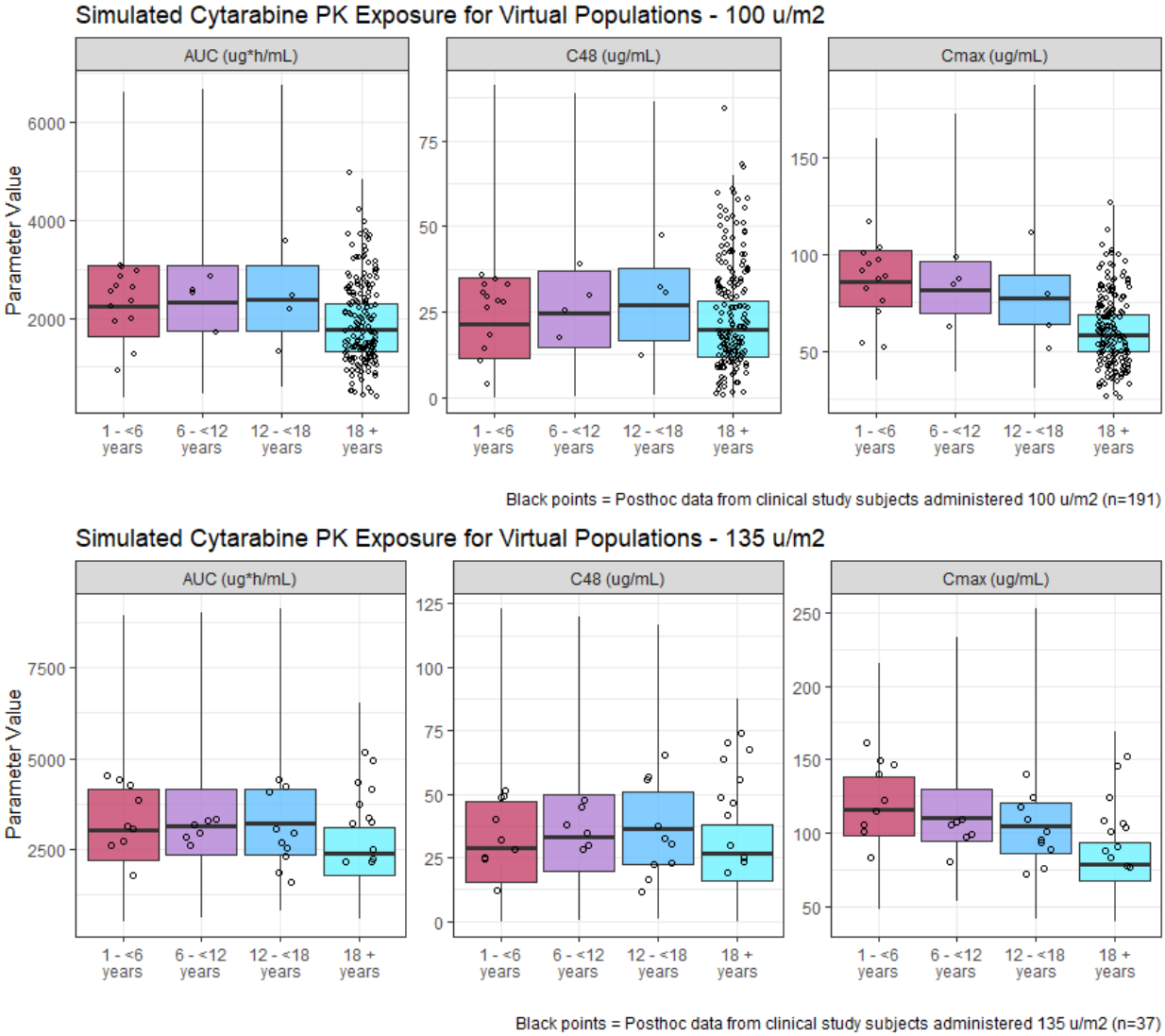
AML-MRC= acute myeloid leukemia with myelodysplasia-related changes; AUC_{48} = area under the curve from time 0 to 48 h following CPX-351 administration on Day 5; C_{max} = maximum concentration following CPX-351 administration on Day 5, C_{48} = concentration 48 h following CPX-351 administration on Day 5; CV= coefficient of variation; n= number of subjects; t-AML= therapy-related acute myeloid leukemia

Source: Table 4, Applicant's Monte Carlo Simulation Report

Reviewer Comments

The Applicant applied the Study effects on CL/F and Vc/F to all virtual subjects in the exposure simulation regardless of age which resulted in lower post hoc CL, lower post hoc Vc, and higher predicted exposure values. However, the underlying cause(s) of the Study effects are uncertain, and it is not clear whether the effects on CL/F and Vc/F are due to differences in the adult and pediatric samples, differences in the clinical studies, or something else entirely. Because the age distribution by study was so discretely divided between pediatric/young adult studies and the adult studies, the reviewer's simulation applied the Study effects to subjects 21 years of age or younger only, to mimic the age distribution by study in the population PK dataset. The resulting cytarabine exposure parameters for this simulation are shown in ***Figure 22.***

Figure 22. Predicted Cytarabine Exposure Parameters for 100 and 135 units/m^2 with Study Effect Applied to Virtual Pediatric and Young Adult Subjects



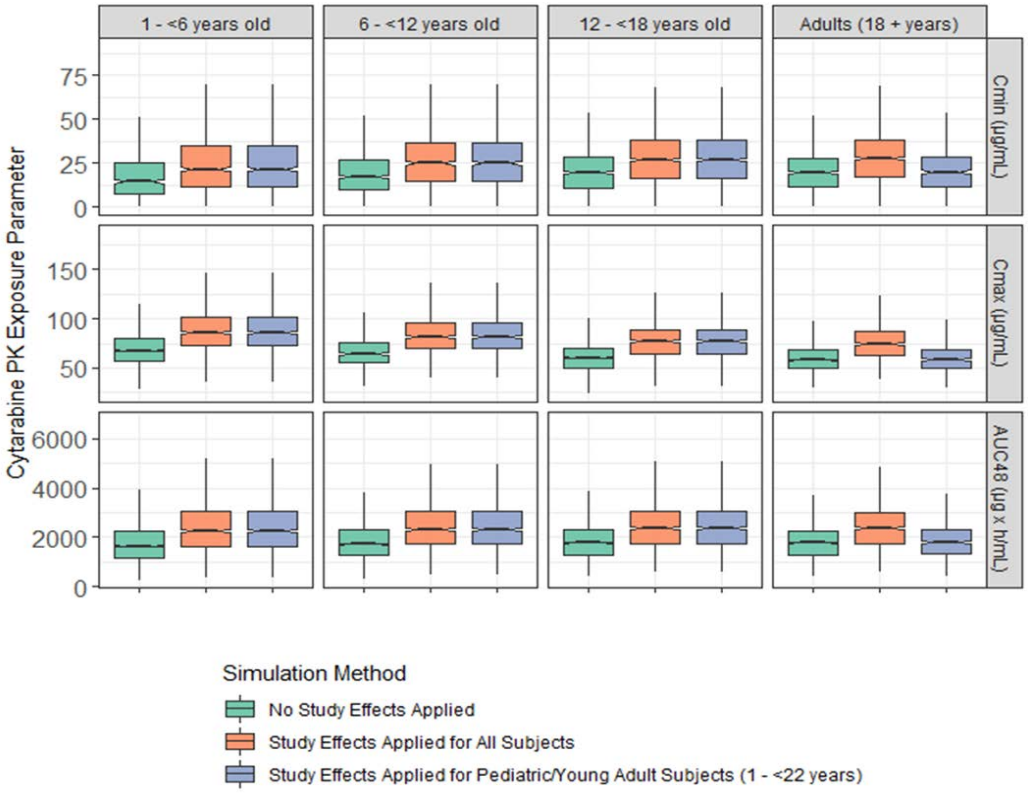
Pediatric and young adult studies included subjects between 1 - <22 years of age; Boxplots = virtual population

exposure according to age groups and dose. Black points = individual estimated exposure from clinical study subjects according to age groups and dose.
Source: Reviewer Analysis

Because the contributing factors for the Study effects on CL/F and Vc/F are not well characterized, reviewer's analysis also summarized the predicted cytarabine exposure for all virtual subjects both with and without the Study effects. Results are shown in ***Figure 23*** *and summarized in* ***Table 26****. This summary demonstrates that whether the Study effects apply to both or neither of the pediatric and adult target population of patients with t-AML or AML-MRC, the cytarabine exposure is not expected to be clinically significant different between any age groups down to 1 year of age. If the Study effect applies only to pediatric subjects and young adults as it did in the population PK model, then 1 - <22 year old subjects are predicted to have higher exposure than adults with the same units/m^2 dose.*

Overall, the results of reviewer's sensitivity analysis support extrapolation of efficacy from adult patients since exposure in pediatrics is expected to be similar to or exceeds exposure in adults. Based on these results, the same dosing regimen of 100 units/m^2 appears reasonable for pediatric patients with t-AML or AML-MRC as recommended for adult patients.

Figure 23. Predicted Exposure Parameters of Cytarabine in Virtual Subjects for 100 units/m^2 With and Without Study Effects



n=1000 per age group per simulation method
Source: Reviewer Analysis

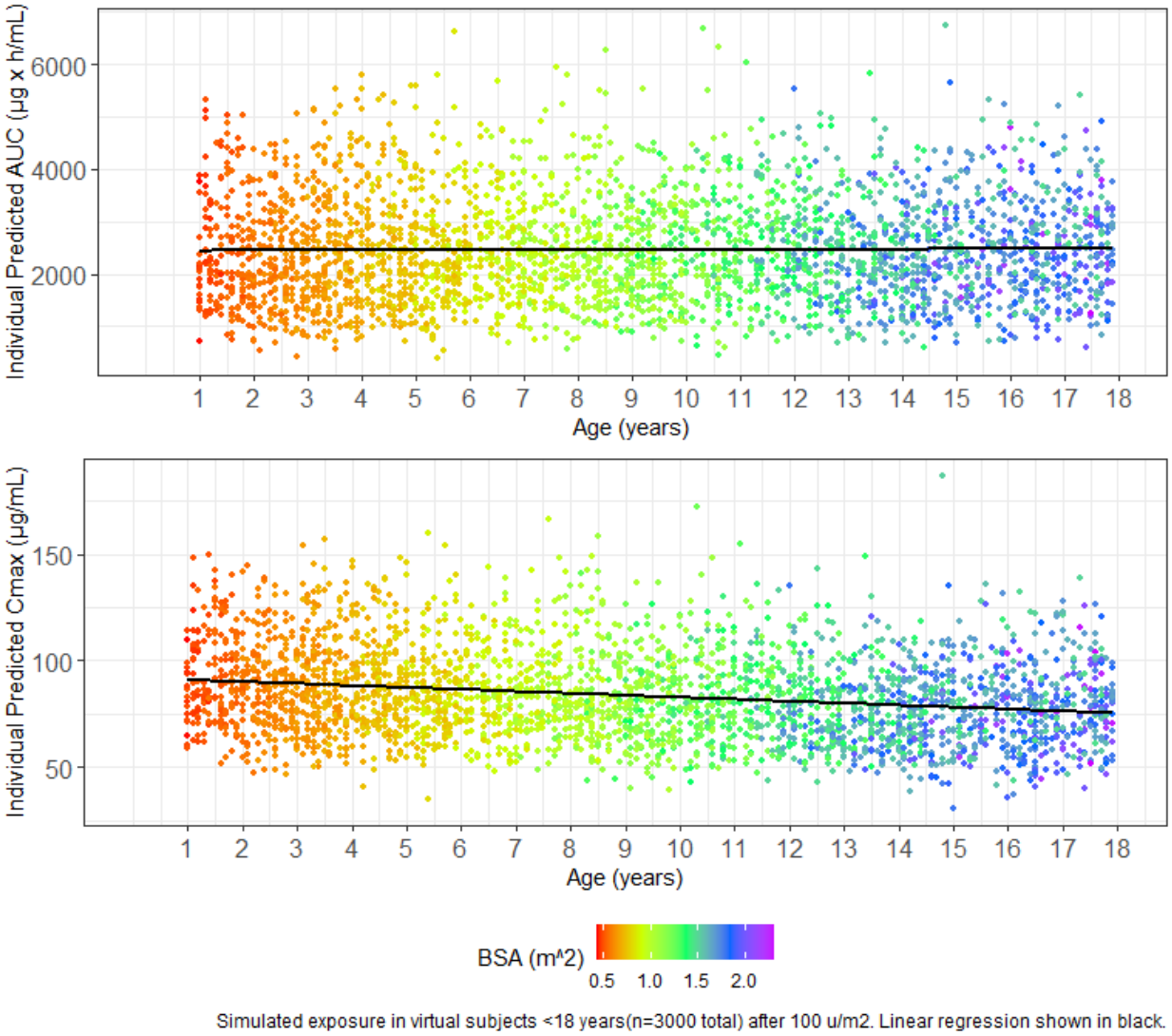
Table 26. Descriptive Statistics of Predicted Exposure Parameters of Cytarabine in Virtual Subjects for 100 units/m^2 with and without Study Effects

Parameter	Statistic	All subjects simulated WITH Study effects on CL and Vc				All subjects simulated WITHOUT Study effects on CL and Vc			
		1 - <6 years old	6 - <12 years old	12 - <18 years old	Adults	1 - <6 years old	6 - <12 years old	12 - <18 years old	Adults
	N	1000	1000	1000	1000	1000	1000	1000	1000
AUC48 (µg x h/mL)	**Mean (CV%)**	2442 (43.4%)	2479 (40.1%)	2462 (39.1%)	2453 (38.5%)	1824 (45.1%)	1870 (42.0%)	1841 (40.6%)	1852 (40.3%)
	GeoMean (GeoCV%)	2217 (47.6%)	2282 (43.7%)	2269 (43.7%)	2271 (41.9%)	1645 (49.1%)	1710 (45.5%)	1687 (45.2%)	1704 (43.8%)
	Median [5th-95th percentile]	2244.91 [1035 - 4450]	2319.19 [1086 - 4245]	2368.37 [1089 - 4199]	2356.62 [1063 - 4175]	1661.68 [750 - 3388]	1736.86 [800 - 3329]	1754.56 [790 - 3198]	1776.53 [782 - 3172]
Cmax (µg/mL)	**Mean (CV%)**	89.0 (24.1%)	83.8 (24.4%)	78.2 (24.4%)	76.8 (25.0%)	70.3 (24.1%)	65.9 (24.6%)	61.2 (24.0%)	60.4 (25.2%)
	GeoMean (GeoCV%)	86.5 (24.3%)	81.4 (24.4%)	76.0 (24.7%)	74.5 (24.7%)	68.3 (24.2%)	64.0 (24.4%)	59.5 (24.3%)	58.6 (24.9%)
	Median [5th-95th percentile]	85.98 [58.9 - 129]	81.32 [54.7 - 121]	77.24 [51.6 - 112]	74.08 [50.9 - 111]	67.96 [46.4 - 101]	63.9 [43.0 - 95.3]	60.05 [40.3 - 87.4]	58.33 [40.1 - 89.4]
C48 (µg/mL)	**Mean (CV%)**	24.6 (68.1%)	26.9 (58.6%)	28.2 (54.5%)	28.5 (52.6%)	17.4 (73.9%)	19.5 (63.7%)	20.3 (59.2%)	20.8 (57.1%)
	GeoMean (GeoCV%)	18.0 (120.3%)	21.2 (99.8%)	23.0 (83.3%)	23.6 (79.9%)	12.0 (139.5%)	14.7 (114.6%)	15.9 (96.8%)	16.6 (91.6%)
	Median [5th-95th percentile]	21.43 [3.44 - 56.1]	24.74 [5.03 - 55.6]	26.82 [5.59 - 55.7]	27.59 [6.08 - 55.2]	14.19 [1.79 - 42.5]	17.72 [2.89 - 42.5]	19.12 [3.34 - 42.0]	19.73 [3.61 - 42.2]

GeoMean = Geometric Mean; GeoCV = Geometric CV
Source: Reviewer Analysis

The youngest simulated age group was 1 - <6 years, and so predicted exposure for virtual subjects was also investigated in terms of age and BSA. Predicted exposure parameters for 100 units/m^2 are displayed by age and BSA for virtual pediatric subjects in ***Figure 24****. The youngest (down to 1 year of age) and smallest (down to 0.42 m^2 BSA) virtual subjects were not predicted to have significant differences in exposure compared to other pediatric and young adult subjects.*

Figure 24. Predicted Cytarabine AUC48 and Cmax for 100 units/m^2 Displayed by Age and BSA for Virtual Subjects 1 - < 18 years



Source: Reviewer Analysis

3. Exposure-Response Analysis

3.1 Exposure-Response Analysis Summary

Cytarabine and daunorubicin exposures were assessed for relationships with safety and efficacy endpoints. Safety analyses were conducted for the pooled adult and pediatric dataset as well as the pediatric/young adult dataset. Efficacy analyses were conducted for the pooled adult and pediatric dataset and for the dataset of adults with newly-diagnosed AML from Study CLTR0310-301.

3.2 Introduction

The primary objectives of the Applicant's analysis were to:

- Perform exposure-response analysis of efficacy endpoints (i.e., complete response [CR], complete response with incomplete platelet or neutrophil recovery [CRi], overall survival [OS] and event-free survival [EFS]) in adult patients with newly diagnosed AML treated with CPX-351 in Study CLTR0310-301. Based on the exposure-response relationship, predict efficacy of CPX-351 in pediatric patients with newly diagnosed t-AML or AML-MRC (100 and 135 units/m^2).
- (b) (4)

3.3 Applicant's Exposure-Response Analysis of Efficacy

3.3.1 Exposure-Response Model in Adults with Newly Diagnosed AML

The exposure-response dataset contained adult subjects in both the active (100 units/m^2 liposomal cytarabine and daunorubicin) and control (7+3 regimen) arms of Study CLTR0310-301 (n = 281). The PK exposure parameter of AUC48 was derived from the population PK model for adult subjects in Study CLTR0310-301 (n = 130). Adult patients in the control arm were assigned an AUC48 value of 0 ug*h/mL (n = 151).

The dataset contained the response endpoints of CR, CRi, OS, and EFS for all subjects. Logistic regression exposure-response models were developed to predict probability of CR or CRi. Parametric time-to-event models were developed to predict OS and EFS. Cytarabine post hoc AUC48, as described above, was used as exposure input for all models.

Reviewer Comments:

The 7+3 treatment administered in the control arm likely included non-liposomal cytarabine and/or daunorubicin. PK concentrations were not measured in the control arm, but these subjects may have had cytarabine and/or daunorubicin AUC48 values that were above zero. This will be addressed in the Reviewer's Independent Analysis (Section 3.4).

3.3.2 Exposure-Response Model-Predicted Efficacy in Virtual Pediatric Patient Populations

Using the CR + CRi, OS, and EFS exposure-response models created from Study CLTR0310-301 adults with newly-diagnosed AML, efficacy endpoints were predicted in the three virtual pediatric populations. The cytarabine population PK model-predicted cytarabine exposure (AUC48) was used as exposure input for virtual pediatric subjects. As shown in **Table 27**, (b) (4) the 100 units/m^2 strength.

Table 27. Predicted Probability of CR and Odds Ratio (135:100 units/m^2) of CR in Pediatric Patients with Newly Diagnosed t-AML or AML-MRC by Age Group

Dose (units/m^2)	Age Group	Predicted Median AUC_{48} (µg.h/mL)	Estimated Probability of CR (%) (95% CI)	Estimated OR of CR (95%CI) 135:100 units/m^2
100	1 – <6 years	2296	42.7 [33.8 - 52.1]	
	6 – <12 years	2355	43.2 [34.0 - 52.8]	
	12 – <18 years	2353	43.2 [34.0 - 52.8]	
135	(b) (4)			

Note 1: 1000 subjects per age group
Note 2: The 95% CI for probability of CR were derived based on parameter uncertainty.
AML-MRC= acute myeloid leukemia with myelodysplasia-related changes; AUC_{48}= area under the curve from time 0 to 48 h following CPX-351 administration on Day 5; CI = confidence interval; CR= complete response; OR = odds ratio; t-AML= therapy-related acute myeloid leukemia

Source: Table 7, Applicant's Monte Carlo Simulation Report

Reviewer Comments

The predicted exposure (cytarabine AUC48) was higher for 135 units/m^2 compared to 100 units/m^2 in the simulated pediatric populations. (b) (4)

(b) (4)

(b) (4)

[redacted]

3.4 Reviewer's Independent Exposure-Response Analysis for Efficacy in Adults with Newly Diagnosed AML

3.4.1 Introduction

Because the Applicant's exposure-response analysis for use with Monte Carlo simulations was performed using response data from both the active arm and control (7+3 regimen) arm of Study CLTR0310-301 while only measuring cytarabine concentrations in the active arm, a sensitivity analysis was performed which only used data from patients who had received liposomal cytarabine and daunorubicin (n=130).

3.4.2 Methods

Efficacy response data for CR and CRi was provided by the Applicant. The cytarabine individual AUC48 estimates were calculated from individual predicted exposure in the Reviewer's analysis with the final cytarabine population PK model. Individual estimates of cytarabine AUC48 ranged from 410.2 ug*h/mL to 4974.1 ug*h/mL in this dataset. Code provided by the Applicant was adapted to perform logistic regression and create figures for analysis. R version 4.0.2 was used for all analysis.

3.4.3 Results

Cytarabine post hoc AUC48 had a significant positive effect on probability of CR (**Table 28** and **Figure 25**) which confirmed this conclusion from the Applicant's analysis. Significance was defined as p-value <0.05 for both intercept and slope in the logistic regression in the Applicant's analysis and Reviewer's Independent Analysis.

For logistic regression of the relationship between cytarabine post hoc AUC48 and probability of CR or CRi, the slope was found to be significant (p-value = 0.0488) but the intercept was not (p-value = 0.0692), as shown in **Table 29** and **Figure 26**.

In summary, the Applicant used exposure-response analysis of cytarabine individual estimated AUC48 and probability of CR in Study CLTR0310-301 subjects (b) (4)

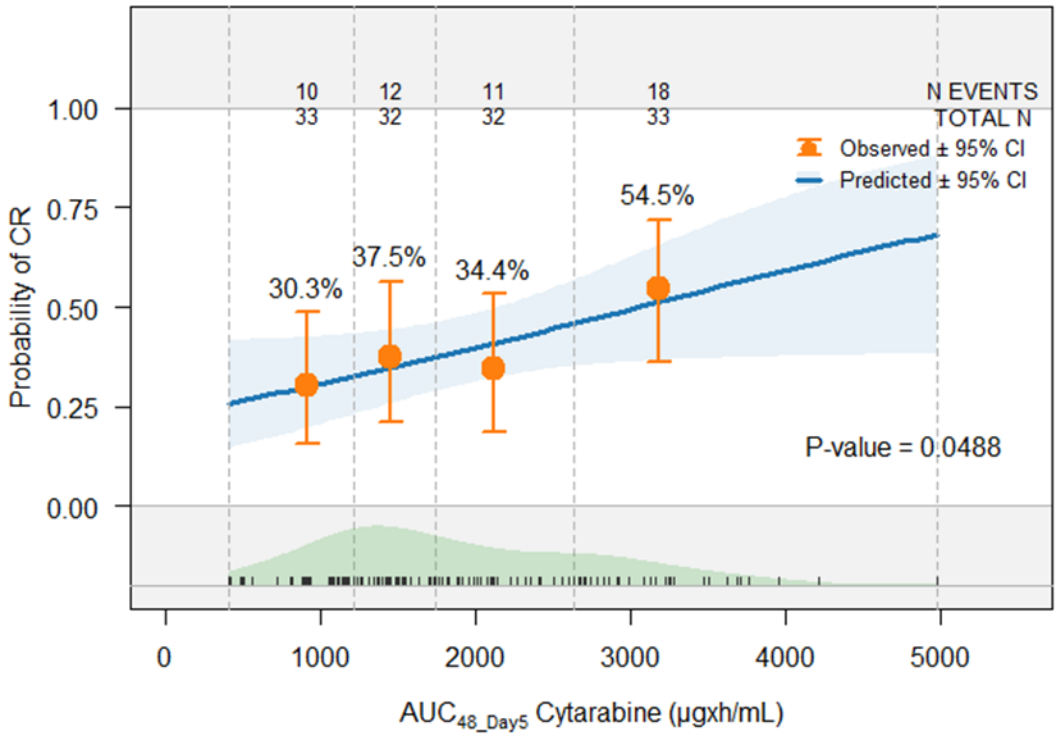
[redacted]

Table 28. Probability of CR in Adult Patients with Newly Diagnosed AML Administered 100 units/m^2 (Study CLTR0310-301 active arm): Logistic Regression Parameter Estimates

Parameter	Estimate	SE	P-value
Intercept	-1.2123	0.4376	0.0056
Slope AUC48 (1000 ug*h/mL increment)	0.3972	0.2016	0.0488

Source: Reviewer Analysis

Figure 25. Probability of CR in Adult Patients with Newly Diagnosed AML Administered 100 units/m^2 (Study CLTR0310-301 active arm): Exposure-Response Relationship



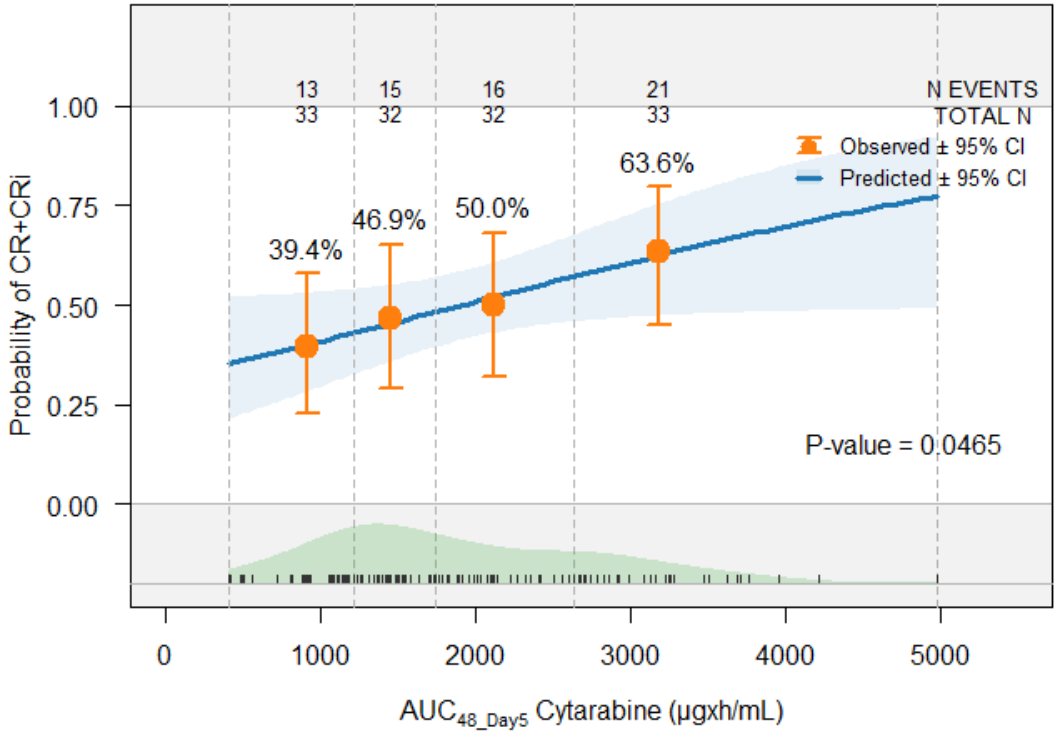
Source: Reviewer Analysis

Table 29. Probability of CR + CRi in Adult Patients with Newly Diagnosed AML Administered 100 units/m^2 (Study CLTR0310-301 active arm): Logistic Regression Parameter Estimates

Parameter	Estimate	SE	P-value
Intercept	-0.7693	0.4233	0.0692
Slope AUC48 (1000 ug*h/mL increment)	0.4017	0.2017	0.0465

Source: Reviewer Analysis

Figure 26. Probability of CR + CRi in Adult Patients with Newly Diagnosed AML Administered 100 units/m^2 (Study CLTR0310-301 active arm): Exposure-Response Relationship



Source: Reviewer Analysis

3.5 Applicant's Exposure-Response Analysis of Safety

3.5.1 Data

The exposure-response analysis of safety included data from children, adolescents, and young adults (Study AAML1421 and Study CPX-MA-1201) as well as data from adults (Study CLTR0305-101, Study CLTR0310-206, and Study CLTR0310-301). A summary of these subjects is listed in **Table 30.** Post hoc PK exposure parameters (AUC48, Cmax, C48) for both cytarabine and daunorubicin in the dataset were predicted by the final cytarabine population PK model and the final daunorubicin population PK model, respectively. The observed Day 5 predose concentration (Cpredose) was also assessed as an exposure parameter for cytarabine and daunorubicin.

Safety endpoints for analysis included incidence of neutropenia, incidence of rash, time to ANC recovery, time to platelet recovery, and incidence of grade 3 to 5 treatment emergent adverse events (TEAEs). Grade 3-5 TEAEs were assessed using a dataset listing the highest (i.e., worst) grade AE per individual subject and did not take into account whether a subject had experienced multiple AEs.

Baseline covariates were evaluated for potential risk factors, which included continuous age,

categorical age, sex, bone marrow blast count categories, WBC count, and platelet count.

Table 30. Summary of Clinical Studies Included in Exposure-Safety Datasets

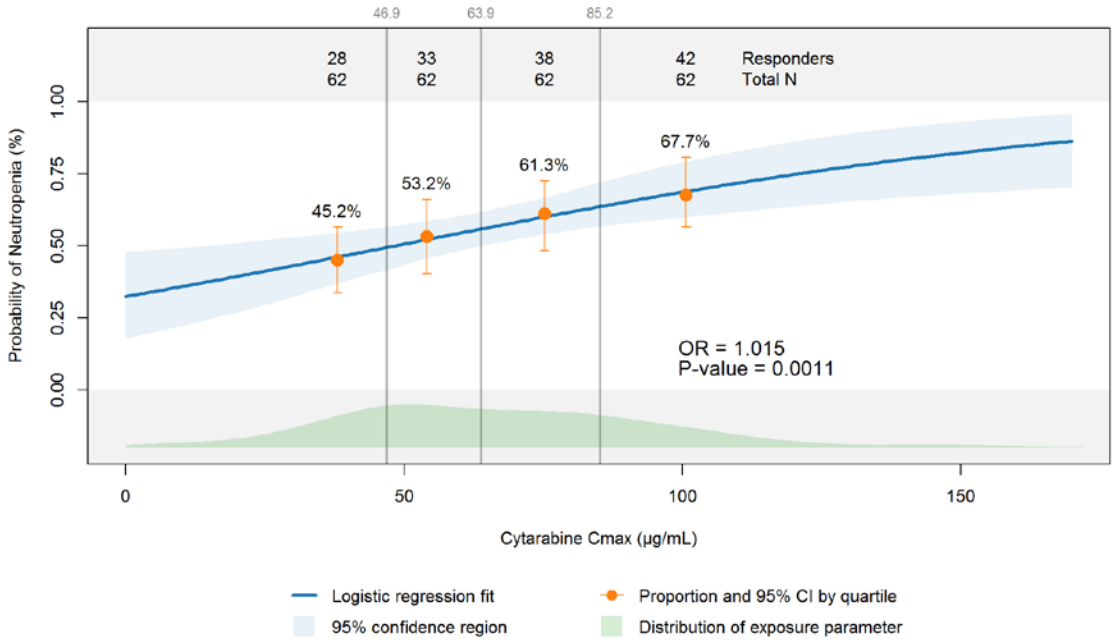
Study	Median Age (Max-Min)	Doses	Subjects with PK Data in safdata.xpt Dataset	Subjects with PK Data in recov1201.xpt and recov1421.xpt Datasets
CLTR0305-101	62.5 years (24 – 81)	3, 6, 12, 24, 32, 43, 57, 76, 100, and 135 u/m²	37	
CLTR0310-206	67.0 years (37 – 80)	100 u/m²	26	
CLTR0310-301	68.0 years (60 – 75)	100 u/m²	130	
CPX-MA-1201	5.0 years (1 – 19)	100 u/m² (n=22) and 135 u/m² (n=5)	27	27
AAML1421	13.0 years (1 – 21)	135 u/m²	28	28

Source: Reviewer Analysis of Applicant's Datasets

3.5.2 Exposure-Response Model Development and Results

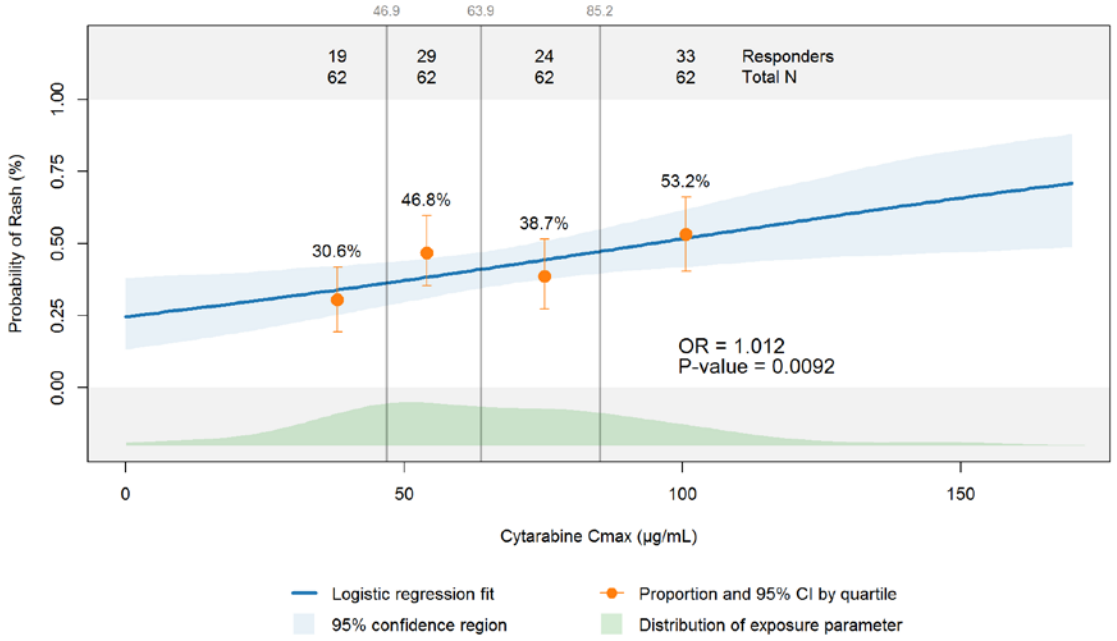
Cytarabine exposure was a statistically significant predictor of the probability of neutropenia events and the probability of rash events in the pooled adult and pediatric dataset (n=248 with 46 subjects younger than 18 years and 202 adults), as shown in **Figure 27** and **Figure 28**. Cytarabine Cmax had better goodness-of-fit compared to AUC48 or C48. No covariates or baseline characteristics had a significant impact on probability of neutropenia or probability of rash when analyzed with the exposure response models using cytarabine Cmax.

Figure 27. Logistic Regression: Probability of Neutropenia as a Function of Cytarabine Cmax on Day 5 in Pooled Pediatric and Adult Safety Dataset



Source: Figure 4, Applicant's Exposure Response Analysis

Figure 28. Logistic Regression: Probability of Rash as a Function of Cytarabine Cmax on Day 5 in Pooled Pediatric and Adult Safety Dataset



Source: Figure 5, Applicant's Exposure Response Analysis

Neither cytarabine nor daunorubicin exposure were significant predictors of time to neutrophil recovery or time to platelet recovery in the pediatric/young adult studies.

In the dataset of 53 pediatric/young adult study subjects and 191 adult patients which only contained one TEAE per subject, the frequency of grade 3 to 5 TEAEs was positively associated with cytarabine Cmax. A similar trend was observed for daunorubicin Cmax.

In the dataset of 53 pediatric/young adult study subjects which only contained one TEAE per subject, neither cytarabine or daunorubicin exposure had a significant relationship with frequency of grade 3 to 5 TEAEs.

Reviewer Comments

The Applicant provided a dataset of all TEAEs recorded for all subjects as well as a dataset of one TEAE per subject listing the worst grade TEAE experienced by that subject. The former was analyzed further in the Reviewer's Independent Analysis (section 3.6).

3.6 Reviewer's Independent Exposure-Response Analysis of Safety

3.6.1 Introduction

In order to investigate potential exposure-response relationships for safety endpoints in pediatrics and young adults, the Reviewer performed logistic regression for neutropenia incidence and rash incidence in the safety dataset of subjects in Study AAML-1421 and Study CPX-MA-1201 (n = 55).

Additionally, the Applicant summarized and assessed TEAEs with use of a dataset which listed only the highest grade TEAE per subject, so it did not account for multiple TEAEs of different grades or severities experienced by the same subject. To provide more information on safety, the frequency of any TEAE and TEAE incidence by grade were assessed using a dataset of all TEAEs which contained records of multiple TEAEs per subject. TEAE incidence was also assessed according to age category as well as post hoc PK exposure.

3.6.2 Methods

For assessment of neutropenia incidence and rash incidence, the safety dataset and code for logistic regression provided by the Applicant were reviewed and then utilized with the safety dataset of subjects in Study AAML-1421 and Study CPX-MA-1201. Exposure parameters (AUC48, Cmax, and C48) were calculated by the Applicant using individual predicted concentrations from the final cytarabine and final daunorubicin population PK models and included in the safety dataset for each subject.

For assessment of TEAEs, the complete TEAE dataset was provided by the Applicant. This dataset did not include TEAEs determined to be "not related" to treatment. The Applicant provided code for summarizing TEAE incidence in the worst-grade-by-subject dataset, and this code was adapted to summarize the complete TEAE dataset. R version 4.0.2 was used for all analysis.

3.6.3 Results

The results of the Reviewer's analysis of neutropenia incidence and rash incidence in the pediatric/young adult studies using logistic regression are listed in **Table 31.** No significant exposure-response relationship was identified for any cytarabine or daunorubicin exposure parameters and safety endpoints of rash or neutropenia incidence.

Table 31. Analysis of Exposure-Response for Neutropenia Incidence and Rash Incidence in Pediatric/Young Adult Studies

Response parameter	Exposure parameter	Odds Ratio
Probability of neutropenia	Cytarabine C48 (ug/mL)	1.005 (p-value = 0.7806)
	Cytarabine Cmax (ug/mL)	0.997 (p-value = 0.7974)
	Cytarabine AUC48 (ug*h/mL)	1.000 (p-value = 0.9878)
	Daunorubicin C48 (ug/mL)	0.973 (p-value = 0.6439)
	Daunorubicin Cmax (ug/mL)	0.977 (p-value = 0.3815)
	Daunorubicin AUC48 (ug*h/mL)	0.999 (p-value = 0.3422)
Probability of rash	Cytarabine C48 (ug/mL)	0.995 (p-value = 0.7775)
	Cytarabine Cmax (ug/mL)	1.005 (p-value = 0.6591)
	Cytarabine AUC48 (ug*h/mL)	1.000 (p-value = 0.9503)
	Daunorubicin C48 (ug/mL)	0.974 (p-value = 0.647)
	Daunorubicin Cmax (ug/mL)	1.000 (p-value = 0.9968)
	Daunorubicin AUC48 (ug*h/mL)	1.000 (p-value = 0.8005)

Source: Reviewer Analysis

The summary of TEAEs according to age group is listed in **Table 32.** No clear trend was observed between age group and number of subjects who experienced grade 3-5 TEAEs or number of subjects who experienced TEAEs (any grade).

The frequency of TEAEs according to cytarabine post hoc Cmax quartile is summarized in **Table 33** for the pooled dataset of adults and pediatric subjects. There was a trend of increasing number of subjects who experienced a grade 3 to 5 TEAE as exposure increased from the 1st to 4th quartile of individual estimated Cmax. However, there was not a clear trend between exposure and number of subjects who experienced TEAEs (any grade).

The cytarabine post hoc Cmax range was narrower and the median was higher in the pediatric and young adult study subjects compared to the population PK dataset as a whole, likely due to the fact that the pediatric and young adult studies only administered two strengths (100 and 135 units/m^2) while the adult studies administered multiple strengths between 3 and 135 units/m^2. The frequency of TEAEs according to cytarabine post hoc Cmax quartile are summarized in **Table 34** for the subjects in pediatric/young adult studies (AAML-1421 and CPX-MA-1201). No clear trend was observed between exposure and number of subjects who experienced grade 3-5 TEAEs or number of subjects who experienced TEAEs (any grade).

Table 32. Treatment-Emergent Adverse Events by Grade and Age Category

	1 - <6 years old N (%)	**6 - <12 years old N (%)**	**12 - <18 years old N (%)**	**Adults N (%)**
Subjects	21	9	13	189
TEAE NCI-CTC Grade				
1	7 (33.3%)	0 (%)	2 (15.4%)	165 (87.3%)
2	7 (33.3%)	1 (11.1%)	6 (46.2%)	142 (75.1%)
3	21 (100%)	9 (100%)	12 (92.3%)	135 (71.4%)
4	16 (76.2%)	3 (33.3%)	6 (46.2%)	27 (14.3%)
5	0 (%)	0 (%)	0 (%)	3 (1.6%)
3-5	21 (100%)	9 (100%)	12 (92.3%)	142 (75.1%)
Any grade	21 (100%)	9 (100%)	13 (100%)	189 (100%)
TEAEs by Severity				
Experienced serious TEAE	5 (23.8%)	4 (44.4%)	3 (23.1%)	52 (27.5%)
Did not experience serious TEAE	16 (76.2%)	5 (55.6%)	10 (76.9%)	137 (72.5%)

N (%) = Number of subjects who had TEAE (percentage of subjects who had TEAE); NCI-CTC= National Cancer Institute – comment toxicity criteria
Source: Reviewer Analysis of Applicant's Dataset

Table 33. Treatment-Emergent Adverse Events by Grade and Exposure Category (Individual Estimated Cytarabine Cmax)

	Cmax 2.21 to 46.9 ug/mL N (%)	**Cmax 46.9 to 63.4 ug/mL N (%)**	**Cmax 63.4 to 84.9 ug/mL N (%)**	**Cmax 84.9 to 161 ug/mL N (%)**	**Overall N (%)**
N	54	59	61	58	232
TEAE NCI-CTC Grade					
1	45 (83.3%)	50 (84.7%)	48 (78.7%)	31 (53.4%)	174 (75%)
2	37 (68.5%)	45 (76.3%)	41 (67.2%)	33 (56.9%)	156 (67.2%)
3	34 (63%)	42 (71.2%)	47 (77%)	54 (93.1%)	177 (76.3%)
4	7 (13%)	13 (22%)	14 (23%)	18 (31%)	52 (22.4%)
5	1 (1.9%)	1 (1.7%)	1 (1.6%)	0 (%)	3 (1.3%)
3-5	36 (66.7%)	44 (74.6%)	49 (80.3%)	55 (94.8%)	184 (79.3%)
Any grade	54 (100%)	59 (100%)	61 (100%)	58 (100%)	232 (100%)
Severity					
Experienced serious TEAE	13 (24.1%)	14 (23.7%)	19 (31.1%)	18 (31%)	64 (27.6%)
Did not experience serious TEAE	41 (75.9%)	45 (76.3%)	42 (68.9%)	40 (69%)	168 (72.4%)

N (%) = Number of subjects who had TEAE (percentage of subjects who had TEAE); NCI-CTC= National Cancer Institute – comment toxicity criteria
Source: Reviewer Analysis of Applicant's Dataset

Table 34. Treatment-Emergent Adverse Events by Grade and Exposure Category (Individual Estimated Cytarabine Cmax) in Pediatric/Young Adult Studies

	Cmax 51.0 to 82.0 ug/mL N (%)	**Cmax 82.0 to 96.9 ug/mL N (%)**	**Cmax 96.9 to 111.2 ug/mL N (%)**	**Cmax 111.2 to 152.1 ug/mL N (%)**	**Overall *N (%)***
N	13	12	13	11	49
TEAE NCI-CTC Grade					
1	1 (7.7%)	2 (16.7%)	1 (7.7%)	5 (45.5%)	9 (18.4%)
2	3 (23.1%)	6 (50%)	3 (23.1%)	3 (27.3%)	15 (30.6%)
3	12 (92.3%)	12 (100%)	13 (100%)	11 (100%)	48 (98.0 %)
4	9 (69.2%)	8 (66.7%)	5 (38.5%)	4 (36.4%)	26 (53.1%)
5	0 (%)	0 (%)	0 (%)	0 (%)	0 (0%)
3-5	12 (92.3%)	12 (100%)	13 (100%)	11 (100%)	48 (98.0 %)

	Cmax 51.0 to 82.0 ug/mL N (%)	**Cmax 82.0 to 96.9 ug/mL N (%)**	**Cmax 96.9 to 111.2 ug/mL N (%)**	**Cmax 111.2 to 152.1 ug/mL N (%)**	**Overall *N (%)***
Any grade	13 (100%)	12 (100%)	13 (100%)	11 (100%)	49 (100%)
TEAEs by Severity					
Experienced serious TEAE	3 (23.1%)	3 (25%)	6 (46.2%)	5 (45.5%)	17 (34.7%)
Did not experience serious TEAE	10 (76.9%)	9 (75%)	7 (53.8%)	6 (54.5%)	32 (65.3%)

N (%) = Number of subjects who had TEAE (percentage of subjects who had TEAE); NCI-CTC= National Cancer Institute – comment toxicity criteria
Source: Reviewer Analysis of Applicant's Dataset

4. Listing of reviewer analyses codes and output files

File.Name	**Description**	**Location in \\cdsnas\pharmacometrics**
.mod and .lst files for run 001 - run 014	Reviewer's Independent Analysis for cytarabine population PK: run 001 – run 014	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\FDA_Review\PPK_Indep_Review_Cytarabine
run103_REK.mod and run103_REK.lst	Simulation of exposure in popPK dataset using post hoc parameters from final cytarabine model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\Monte_Carlo_Sim_Analysis\run 103 simulation REK\nmfe_run103_REK_003
Posthocexposure.csv	Post hoc AUC, Cmax, and C48 for popPK dataset (Applied Study effect on CL and Vc to pediatric/ young adult study subjects)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\Monte_Carlo_Sim_Analysis\run 103 simulation REK
Population_PK_Review_Template_NDA209401_cytarabine_and_daunorubicin.rmd and .docx	R markdown code and .docx output for analyzing popPK datasets, popPK models, and simulation datasets; code for Table 19,Table 23, Figure 13, Figure 14, Figure 15, Figure 19, Figure 20, Figure 21	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\FDA_Review
"Plotting Posthoc Exposure.rmd" and "Plotting-Posthoc-Exposure.docx"	R markdown code and .docx output to analyze post hoc PK exposure from final cytarabine popPK model (includes age, race comparisons); code for Figure 16, Figure **17**, Table 21	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\Monte_Carlo_Sim_Analysis
Pmx-Review-of-sim_all-sponsor-code.rmd and .docx	R markdown code and .docx output for analysis of Applicant PK simulation code and simulation of PK exposure	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\Monte_Carlo_Sim_Analysis

File.Name	Description	Location in \\cdsnas\pharmacometrics\
	with and without Study Effects; code for Table 26, Figure 22, Figure 23, Figure 24	
CR_CRi_Review_ReviewerData.rmd and .docx	R markdown code and .docx output to analyze Phase 3 adult exposure-efficacy; code for Figure 25, Figure 26, Table 28, Table 29	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\Monte_Carlo_Sim_Analysis\ER_Efficacy_CR_CRi_Review
Review_Rash_Neutropenia_Incidence.rmd and .docx	R markdown code and .docx output to analyze Applicant code for rash and neutropenia E-R incidence; analysis of rash and neutropenia E-R in pediatric studies; code and data for Table 31	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\ER_Analysis\Review_of_Rash_Neutropenia_Incidence
Review_TEAE.rmd and .html	R markdown code and .html output to analyze Applicant code for E-R analysis of TEAE frequency; analysis of TEAE frequency E-R in pooled and pediatric datasets; code and data for Table 32, Table 33, Table 34	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CytarabineDaunorubicinLiposome_sNDA209401_S006_REK\ER_Analysis \Review_of_TEAEs

14.5 Additional Clinical Outcomes Assessment Analyses

None.

15 DIVISION DIRECTOR (DHM1)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

R. Angelo de Claro, MD
Director, Division of Hematologic Malignancies 1 (DHM1)

NDA Multidisciplinary Review and Evaluation
NDA 209401 S-006
Vyxeos® (daunorubicin and cytarabine) liposome

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lauren Price, PhD	OCP/DCPI	Sections: 6, 14	X Authored Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lauren Price -S, 0.9.2342.19200300.100.1.1=2001978474 Date: 2021.03.10 09:15:37 -05'00'			
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6, 14	Authored X Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S Date: 2021.03.10 10:52:46 -05'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 14	Authored X Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1=1300137436 Date: 2021.03.10 18:47:36 -05'00'			
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 14	X Authored Approved
	Signature: Robyn E. Konicki -S Digitally signed by Robyn E. Konicki -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002409730, cn=Robyn E. Konicki -S Date: 2021.03.10 12:04:15 -05'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 14	Authored X Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.03.10 12:49:14 -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 2021.03.11 12:33:23 -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 2021.03.09 09:22:10 -05'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, ACNP	OOD	Sections: 11	X Authored Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.03.11 14:12:03 -05'00'			

NDA Multidisciplinary Review and Evaluation
NDA 209401 S-006
Vyxeos® (daunorubicin and cytarabine) liposome

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 5, 12	X Authored Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	R. Angelo de Claro, 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
03/30/2021 06:53:06 AM

ROMEO A DE CLARO
03/30/2021 07:33:36 AM