24 March 2022
EMA/665588/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyxeos liposomal

International non-proprietary name: daunorubicin / cytarabine

Procedure No. EMEA/H/C/004282/II/0018/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

7 + 3	7-day continuous infusion of cytarabine at a dose of 100 to 200 mg/m2/day in combination with administration of an anthracycline for 3 days
AE	adverse event
AESI	adverse events of special interest
AML	acute myeloid leukemia
AML-MRC	AML with myelodysplasia-related changes
ANC	absolute neutrophil count
Ara-U	1-β-d-arabinofuranosyluracil
AUC	area under the plasma concentration-time curve
BSA	body surface area
CCH	Cincinnati Children's Hospital
CL	clearance
Cmax	maximum concentration
COG	Children's Oncology Group
CPX-351	daunorubicin and cytarabine powder for concentrate for solution for infusion
CR	complete remission
CR1	first complete remission
CR2	second complete remission
CRF	case report form
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CSR	clinical study report
DLT	dose limiting toxicity
DNX	daunoxome
ECG	electrocardiogram
ECHO	echocardiogram
EEA	European Economic Area
EFS	event-free survival
EMA	European Medicines Agency
ERA	Environmental risk assessment
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
PEC	Predicted environmental concentration
FLAG	fludarabine, cytarabine, and G-CSF
FLAG-IDA	FLAG in combination with idarubicin
Fpen	Market penetration
G-CSF	granulocyte-colony stimulating factor

HSCT	hematopoietic stem cell transplant
IV	intravenous
log P	Octanol-water partition coefficient
LVEF	left ventricular ejection fraction
LVSF	left ventricular shortening fraction
MEC	mitoxantrone, cytarabine and etoposide
MLFS	morphologic leukemia-free state
MTD	maximum tolerated dose
ORR	overall response rate
OS	overall survival
PBRER	Periodic Benefit-risk Evaluation Report
PIP	pediatric investigational plan
PK	pharmacokinetic(s)
PT	preferred term
RP2D	recommended phase 2 dose
RR-AML	relapsed or refractory AML
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event
t-AML	therapy-related AML
UK	United Kingdom
US	United States

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Jazz Pharmaceuticals Ireland Limited submitted to the European Medicines Agency on 26 November 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Extension of indication to add treatment of relapsed/refractory AML in paediatric patients with subsequent updates to Sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC based on the new safety and efficacy data from the paediatric clinical study AAML1421. The Package leaflet is updated accordingly. The RMP version 1.1 has also been submitted. In addition, the PI is updated in line with the latest QRD template 10.2. Submission of the final data from paediatric clinical study CPX-MA-1201 in support of the extension of indication.

However, during the procedure the marketing authorisation holder revised the requested scope of the variation and no longer sought an extension of the indication, instead proposing inclusion of relevant paediatric data in the product information based on results from study AAML1421. See Section 4. for details.

Information relating to orphan designation

Vyxeos liposomal, was designated as an orphan medicinal product (EU/3/11/942) on 11 January 2012 in the following indication: Treatment of acute myeloid leukaemia.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-001858-PIP02-16-M03 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001858-PIP02-16-M03 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	26 November 2020
Start of procedure:	20 February 2021
CHMP Rapporteur Assessment Report	16 April 2021
CHMP Co-Rapporteur Assessment Report	22 April 2021
PRAC Rapporteur Assessment Report	22 April 2021
PRAC members comments	28 April 2021
Updated PRAC Rapporteur Assessment Report	29 April 2021
PRAC Outcome	6 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 May 2021
Request for supplementary information (RSI)	20 May 2021
CHMP Rapporteur Assessment Report	12 October 2021
PRAC Rapporteur Assessment Report	13 October 2021
PRAC members comments	20 October 2021
Updated PRAC Rapporteur Assessment Report	21 October 2021
PRAC Outcome	28 October 2021
CHMP members comments	29 October 2021
Updated CHMP Rapporteur Assessment Report	4 November 2021
Request for supplementary information (RSI)	11 November 2021
CHMP Rapporteur Assessment Report	22 February 2022
PRAC Rapporteur Assessment Report	22 February 2022

Timetable	Actual dates
PRAC members comments	02 March 2022
Updated PRAC Rapporteur Assessment Report	3 March 2022
PRAC Outcome	10 March 2022
CHMP members comments	14 March 2022
Updated CHMP Rapporteur Assessment Report	17 March 2022
Opinion	24 March 2022

1.3. Introduction

1.3.1. Problem statement

Vyxeos liposomal is approved for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

State the claimed the therapeutic indication

The MAH is proposing the following extension of the approved AML indication: the treatment of relapsed or refractory AML in paediatric and young adult patients aged 1 to 21 years old.

Clinical presentation, diagnosis and stage/prognosis

Acute myeloid leukaemia is a form of leukaemia – i.e., cancer of the white blood cells – characterised by infiltration of proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated haematopoietic cells of myeloid lineage in the bone marrow, blood, and other tissues.

In AML, leukaemic blasts replace normal blood cells in bone marrow and peripheral blood, which leads to anaemia, neutropenia, and thrombocytopenia. This is associated with symptoms of fatigue, shortness of breath, disturbed wound healing, infections and bleedings. If left untreated, AML results in death within a few weeks to months.

AMLs are classified according to the World Health Organisation (WHO) classification from 2001, revised in 2008 and in 2016 (2). The classification incorporates morphological criteria, cytogenetic data, molecular genetics, immunophenotype data and clinical information into a diagnostic algorithm to delineate clinically significant disease entities.

Management

Leukaemia accounts for approximately 30% of all paediatric malignancies, of which 15–20% comprises AML. Long-term survival rates of pediatric AML patients are currently 70% or even higher. Compared to adults, children with AML have superior outcomes due to fewer adverse genetic mutations and the ability to tolerate the high-intensity chemotherapy currently necessary for cure. Regarding novel agents and treatment modalities, drugs such as venetoclax, monoclonal antibodies, and cellular therapies are investigated in AML.

Treatment decisions, namely the need for hematopoietic stem-cell transplantation (HSCT) in pediatric AML are primarily driven by genetic risk classification which is quickly evolving. However, in 24 - 40% of children the AML relapses, with a probability of long-term survival of approximately 40%. These poor outcomes indicate the need for improved treatment, including innovative drugs and treatment modalities. Due to a relatively small patient population, studies on pediatric relapsed AML mostly consist of case reports and only a few large cohort-based studies have been performed.

For patients who relapse, or are refractory to first-line therapy, there is a limited number of effective therapeutic agents available. Optimal treatment for paediatric relapsed AML is not well defined, regarding optimal chemotherapy, the need for allogeneic HSCT (allo-HSCT), the timing of an allo-HSCT and risk group stratified treatment based on prognostic factors. However, allo-HSCT in the second complete remission after reinduction chemotherapy is associated with better outcome than chemotherapy only, and once a paediatric patient relapses, working towards an allo-HSCT is currently a rule.

1.3.2. About the product

Vyxeos liposomal is a liposomal formulation of a fixed combination of daunorubicin and cytarabine in a 1:5 molar ratio. The 1:5 molar ratio has been shown in vitro and in vivo to maximise synergistic antitumour activity in AML.

Daunorubicin has antimitotic and cytotoxic activity, which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity, inhibiting DNA polymerase activity, affecting regulation of gene expression, and producing DNA-damaging free radicals.

Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5-triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA synthesis. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to proliferating mammalian cells in culture.

Based on data in animals, Vyxeos liposomes accumulate and persist in high concentration in the bone marrow, where they are preferentially taken up intact by leukaemia cells in an active engulfment process. In leukaemia-bearing mice, the liposomes are taken up by leukaemia cells to a greater extent than by normal bone marrow cells. After internalisation, Vyxeos liposomes undergo degradation, releasing daunorubicin and cytarabine within the intracellular environment, enabling the medicinal products to exert their synergistic antineoplastic activity.

The currently approved indication is the treatment of adults with newly-diagnosed therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

1.3.3. The development programme/compliance with CHMP guidance/scientific advice

No scientific advice was given by CHMP with regard to paediatric studies CPX-MA-1201, AAML1421 and 1831.

A paediatric investigational plan (PIP) for CPX-351 (EMA-001858-PIP01-15) was approved on 23 June 2018 (P/0200/2017). There have been 3 PIP modifications submitted to the EMA. The current PIP strategy

includes Study CPX-MA-1201, and Study AAML1421, which are both included in this application. It also includes a newly initiated paediatric Study 1831 in paediatrics patients with newly-diagnosed AML.

1.3.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

No scientific advice was given by CHMP with regard to paediatric studies CPX-MA-1201, AAML1421 and 1831.

A paediatric investigational plan (PIP) for CPX-351 (EMA-001858-PIP01-15) was approved on 23 June 2018 (P/0200/2017). There have been 3 PIP modifications submitted to the EMA. The current PIP strategy includes Study CPX-MA-1201, and Study AAML1421, which are both included in this application. It also includes a newly initiated paediatric Study 1831 in paediatrics patients with newly-diagnosed AML.

A PIP compliance report was approved by PDCO 29.1.2021 (EMA/656343/2020).

1.4. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

1.4.1. Ecotoxicity/environmental risk assessment

The MAH submitted an updated ERA for Vyxeos liposomal according to the active CHMP "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" and the Questions and Answers on the Guideline (EMEA/CHMP/SWP/4447/00 corr2, 2006; EMA/CHMP/SWP/44609/2010 Rev., 2016). It includes both active components of Vyxeos liposomal (cytarabine and daunorubicin) and updates regarding the dosing regimen in adults and the addition of the paediatric population to include the sought paediatric indication in relapsed/refractory (R/R) AML.

Phase I: Estimation of Exposure

Screening for Persistence, Bioaccumulation, and Toxicity

The octanol-water partition coefficient (log Kow log P) of cytarabine was determined by the shake-flask method. The log Kow of cytarabine at 21°C, determined for 3 different water:octanol ratios from 0.5 to 2 using the shake flask method, was determined to be -2.02 ± 0.04. For daunorubicin, the experimental value of log Kow reported in the literature is 1.83. The experimental log Kow values for the drug substances cytarabine and daunorubicin are below 4.5; therefore, further screening is not considered necessary for persistence, bioaccumulation, and toxicity.

Calculation of the Predicted Environmental Concentration (PEC)

Only a maximum number of doses of Vyxeos liposomal can be received over a lifetime by adult patients (n=9 doses), and by children and adolescent patients (n=3 doses) according to the approved and proposed labelling. The use of daunorubicin (and other anthracycline preparations) as monotherapy is also limited

primarily due to the intrinsic cardiotoxicity associated with daunorubicin, one of Vyxeos liposomal active components. Therefore, the fraction of market penetration (Fpen) calculations accounts for the limited number of doses that can be received by patients over their lifetime. The predicted environmental concentration (PEC) was calculated for each of the active components (cytarabine and daunorubicin) for the adults and children/adolescent patient populations separately, and was then be summed to obtain the overall PEC. The Fpen was refined based on prevalence of the disease and treatment regime among each patient population.

Adult Patients

The approved regimen for Vyxeos liposomal is 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine on days 1, 3, and 5 for the first induction; 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine on days 1 and 3, for the second induction; and 29 mg/m^2 daunorubicin and 65 mg/m^2 cytarabine on days 1 and 3 for up to 2 consolidation cycles. The maximum lifetime number of doses in adults is 9 (5 induction doses and 4 consolidation doses), corresponding to a total maximum lifetime dose of 336 mg/m^2 daunorubicin and 760 mg/m^2 cytarabine. Using a maximum body surface area of 2.5 m^2 these doses correspond to 840 mg daunorubicin and 1900 mg cytarabine.

Fpen Calculation

Fpen was calculated using the formula given in EMA/CHMP/SWP/44609/2010 Rev., 2016 and yearly incidence of disease (39881 cases in 2017, a conservative assumption that includes all adult AML patients).

Fpen Daunorubicin = 1.9×10^{-6}

Fpen Cytarabine = 1.9×10^{-6}

PEC_{SW} Calculation

Because the doses used for the induction and consolidation cycles are different, the defined daily dose is the average of the maximum total dose (i.e., induction plus consolidation) divided by the maximum total of dosing days (for daunorubicin 840 mg/9 days = 93.3 mg/day and for cytarabine 1900 mg/9 days = 211.1 mg/day).

Using the formula given in EMEA/CHMP/SWP/4447/00 corr 2:

PEC_{SW} Daunorubicin = 0.000090 µg/L

PEC_{SW} Cytarabine = 0.00020 µg/L

Paediatric Patients

In children and adolescents, the regimen consists of a single induction cycle with 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine on days 1, 3, and 5. Therefore, the maximum number of lifetime doses in children is 3 (3 induction doses) for a maximum total dose of 177 mg/m^2 daunorubicin and 405 mg/m^2 cytarabine. Assuming a body surface area of 2 m^2 the maximum daily doses on dosing days are 118 mg daunorubicin and 270 mg cytarabine.

Fpen Calculation

Fpen was calculated using the formula given in EMA/CHMP/SWP/44609/2010 Rev., 2016 and yearly incidence of disease (R/R paediatric AML yearly incidence is estimated to a maximum of 40% of 2 cases per million inhabitants, or approximately 410 cases per year and a conservative assumption that all paediatric R/R AML patients take Vyxeos liposomal).

Fpen Daunorubicin = 6.6×10^{-9}

Fpen Cytarabine = 6.6×10^{-9}

PEC_{SW} Calculation

Because the doses used for the induction cycles in children are constant, it corresponds to the defined daily dose.

Using the formula given in EMEA/CHMP/SWP/4447/00 corr 2:

PEC_{SW} Daunorubicin = 0.00000039 µg/L

PEC_{SW} Cytarabine = 0.00000089 µg/L

Daunorubicin Use with Other Patients

The QuintilesIMS database search provided an estimate of daunorubicin use (in mg) from 23 different European Union countries for 2Q2017. The QuintilesIMS used data for daunorubicin for 1 quarter (37390 mg), which was then multiplied by 4 in order to predict the yearly use of daunorubicin (149560 mg) in medicinal products other than Vyxeos liposomal. Based on the SmPC for Cerubidin 20 mg Powder for Solution for Injection (daunorubicin hydrochloride), daunorubicin is used for the induction of remission in acute lymphoblastic or lymphatic leukaemias (ALL) and acute myeloid leukaemias (AML). The maximum lifetime cumulative dose for daunorubicin is 550 mg/m^2 due to the potential for cardiotoxicity. Per the SmPC, the recommended daily dose in adults is 45 mg/m^2 and the maximum dose is 60 mg/m^2. Assuming a body surface area of 2.5 m^2 the recommended and maximum doses are 112 mg and 150 mg of daunorubicin, respectively for one treatment day.

Fpen Calculation

Fpen was calculated using the formula given in EMA/CHMP/SWP/44609/2010 Rev., 2016, the daily dose of 45 mg/m^2 and consumption of 149560 mg/year.

Fpen Daudorubicin = 1.1×10^{-8}.

PEC_{SWr} Calculation

Using the formula given in EMEA/CHMP/SWP/4447/00 corr 2:

PEC_{SW} Daunorubicin = 0.0000006 µg/L.

Total $PEC_{surfacewater}$

PEC_{SW} Daunorubicin = PEC_{SW} for adults + PEC_{SWr} for children and adolescents + PEC_{SWr} for other use

PEC_{SW} Daunorubicin = 0.000090 µg/L + 0.00000039 µg/L + 0.0000006 µg/L = **0.000091 µg/L**

PEC_{SW} Cytarabine = PEC_{SW} for adults + PEC_{SW} for children and adolescents

PEC_{SW} Cytarabine = 0.00020 µg/L + 0.00000089 µg/L = **0.00020 µg/L**

Therefore, the PEC_{SW} for either drug substances are below the action limit threshold of 0.01 µg/L and a Phase II environmental-fate and effect analysis is not required.

1.4.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of daunorubicin and cytarabine.

Considering the above data, daunorubicin and cytarabine are not expected to pose a risk to the environment.

1.5. Clinical aspects

1.5.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier Status Report Location Report Type	Type of Study	Study Design and Type of Control	Objective(s) of the Study	Product, Route, Dose and Duration of Treatment	Subject Population Mean age (range)
CPX-MA-1201 Complete Module 5.3.5.2 Full CSR and CSR Erratum	Safety, Efficacy and PK	Phase 1 OL, SC, Pilot study	To determine a safe and tolerable dose of CPX-351 in children and adolescents (≤ 21 years of age) with relapsed or refractory hematopoietic malignancies and to recommend a dose for future studies. To describe the toxicity and tolerability of CPX-351 in children and young adults (≤ 30 years of age) with hematopoietic malignancies. To recommend a dose of CPX-351 for future studies in young patients with previously untreated AML. To describe the PK of plasma cytarabine and daunorubicin after CPX-351 administration to young patients with recurrent or refractory hematologic malignancies.	• CPX-351 100 or 134 units/m^2 by CVC over 90 minutes on Days 1, 3 and 5 • IT cytarabine at the Investigator's discretion in subjects with microscopic disease in CSF and in those at high risk for CNS failure	13 male subjects and 14 female subjects ≥ 1 year and ≤ 21 years for the Dose Exploration Phase and ≥ 1 year and ≤ 30 years for the Expanded Phase with pathologically confirmed relapsed AML or ALL; 6.7 years (1 to 19)

Study Identifier Status Report Location Report Type	Type of Study	Study Design and Type of Control	Objective(s) of the Study	Product, Route, Dose and Duration of Treatment	Subject Population Mean age (range)
AAML1421 Efficacy complete; Follow-up ongoing Module 5.3.5.2 Full CSR	Safety, Efficacy and PK	Phase 1/2 OL, MC	To determine a RP2D and the toxicities associated with CPX-351 in pediatric and young adult subjects with relapsed / refractory AML. To estimate the response rate (CR + CRp) after CPX-351 (Cycle 1) followed by FLAG (Cycle 2) in children with AML in first relapse	*Cycle 1* • 2 doses IT cytarabine (age-based dosing) • CPX-351 135 units/m^2 by CVC over 90 minutes on Days 1, 3 and 5 *Cycle 2* • fludarabine 30 mg/m^2 IV over 30 minutes on Days 1-5. • High dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours on Days 1-5 • 5 µg/kg filgrastim IV or SC on Days 1-5. Dosing was restarted on Day 15 and continued until the post-nadir ANC ≥ 500/µL.	18 male subjects and 20 female subjects with pathologically confirmed relapsed AML; 10.6 (1 to 21)

1.5.2. Pharmacokinetics

Pharmacokinetics in adults

Non-liposomal cytarabine and daunorubicin have markedly different PK parameters from one another. In contrast, when administered as components of daunorubicin and cytarabine powder for concentrate for solution for infusion (referred to thereafter also as CPX-351 in this report), the PK parameters for cytarabine and daunorubicin are similar (**Table 1**). The convergence of PK parameters suggests that most of the cytarabine and daunorubicin in the circulation remains trapped within the liposomes that are slowly eliminated. Therefore, the measured PK parameters for cytarabine and daunorubicin following CPX-351 administration mostly reflect the PK of the liposomes. Small volume of distribution (~7 litres in adults) indicates that the liposomes are highly confined in the vascular space. The accumulation ratio is 1.3 and 1.4 for daunorubicin and cytarabine, respectively, following IV administration at days 1, 3, and 5, consistent with the elimination half-lives.

Table 1. Mean plasma PK parameters for cytarabine and daunorubicin when administered as CPX-351 or as non-liposomal formulations in adult patients.

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

Abbreviations: CL = clearance; $t_{1/2}$ = terminal half-life; V = volume of distribution.

Dose adjustment is not required in elderly patients or in patients with mild or moderate renal impairment. There is no experience in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease. Dose adjustment is not required in patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L.

Pharmacokinetics in the paediatric population

Pharmacokinetics of Vyxeos in the paediatric and young adult population (age 1 to 21 years old, inclusive) were investigated in two clinical trials (CPX-MA-1201 and AAML1421). For both studies, the MAH was not involved in study conduct, but has received the data from the Sponsors and summarized the results of the study for the purposes of regulatory submission. The studies are described in detail in section 5.4 Clinical efficacy of this AR. The PK results are summarised below.

Pharmacokinetic data analysis in individual paediatric studies

In study 1201, the PK Analysis Set included all subjects who received at least 1 infusion of CPX-351 and had at least 1 evaluable PK concentration. This analysis set was used for all descriptive PK summaries.
In study 1421, the PK population includes all patients who received at least one dose of the study drug treatment and provided enough PK samples to estimate at least one PK parameter. The PK analysis was performed using the PK population.

Plasma concentration data used in the PK analyses corresponded to "total" concentrations of cytarabine or daunorubicin, where "total" corresponds to the sum of encapsulated drug (ie, drug retained within the liposomes) plus free drug (i., drug released from the liposomes). Given that >99% of the cytarabine and daunorubicin in the circulation remains encapsulated within the CPX-351 liposomes (see initial marketing authorisation application assessment report), PK analyses based on total plasma concentrations basically describe the plasma kinetics of the encapsulated drugs. The MAH considers PK based on encapsulated drugs relevant to clinical benefits, because uptake of intact liposomes by leukemia cells is central to the mechanism of action for CPX-351 in antileukemic effects.

Plasma concentration-time profiles were generated for cytarabine and daunorubicin for each subject. All plasma PK parameter calculations were performed using actual or nominal times (when actual time was not available), calculated relative to the start of study drug infusion in hours. Concentration values of plasma cytarabine and daunorubicin that were reported as below the limit of quantitation (BLQ) were set to zero for PK parameter calculation and concentration summary statistics.

PK parameters were determined using non-compartmental (NCA) methods based on individual plasma concentration-time data for cytarabine and daunorubicin following Day 5 CPX-351 administration. PK parameters were estimated from the plasma concentration-time profile of all evaluable subjects using non-compartmental methods in Phoenix WinNonlin 7.0 (Pharsight, St. Louis, MO, USA).

Study CPX-MA-1201

Study CPX-MA-1201 was a phase 1 pilot study to assess the PK, toxicity and tolerability of CPX-351 in paediatric and young adult patients (age 1 to 21 years old, inclusive) with relapsed / refractory hematologic malignancies. This study was conducted in two phases: Dose Exploration Phase and Expanded Phase (Table 2).

Table 2. Study design and posology for study CPX-MA-1201

Phase	Treatment	Dose/Regimen	Patients (n)
Exploration	Induction 1	100 units/m^2, Days 1, 3, and 5	4
	Induction 1	134 units/m^2, Days 1, 3, and 5	5
Expanded	Induction 1	100 units/m^2, Days 1, 3, and 5	18

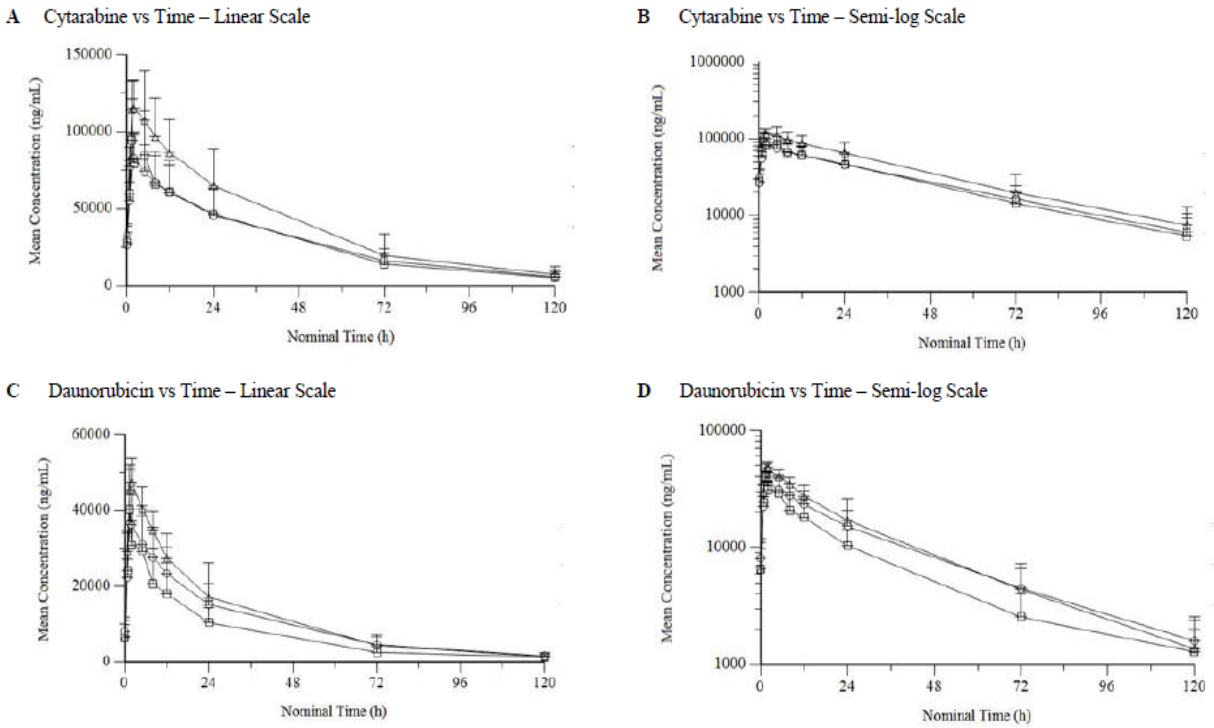
Note: 1 unit CPX-351 = 1 mg cytarabine and 0.44 mg daunorubicin

Blood samples for the determination of the concentrations of plasma cytarabine and daunorubicin were collected following Day 5 infusion, as follows: at predose (0), 45 min, 90 min (end of infusion), 2, 5, 8, 12, 24, 72 and 120 h post start of CPX-351 infusion.

A total of 27 patients were enrolled and included in the PK analysis. No doses were missed on Day 1, Day 3 and Day 5.

At Day 5, peak plasma concentrations of cytarabine and daunorubicin were observed at the end of or soon after the end of infusion. Measurable concentrations were observed until the end of PK follow-up (120 hours after dosing) for both analytes (**Figure 1**). The PK parameters for cytarabine and daunorubicin (calculated using noncompartmental analyses) are summarized in **Table 3**.

Figure 1: Mean (+SD) Plasma Concentrations of Cytarabine and Daunorubicin vs. Time Following a 90 Minute IV Infusion of CPX-351 – Dose Exploration and Expanded Phase (Study CPX-MA-1201)



Notes: Open squares represent mean plasma concentrations for subjects who received 100 units/m^2 CPX-351 during the Dose Exploration Phase. Open triangles represent mean plasma concentrations for subjects who received 134 units/m^2 CPX-351 during the Dose Exploration Phase. Open circles represent mean plasma concentrations for subjects who received 100 units/m^2 CPX-351 during the Expanded Phase.

Table 3. Geometric Mean (CV%) Plasma PK Parameters of Cytarabine and Daunorubicin Following a 90 Minute IV Infusion of CPX-351 (Study CPX-MA-1201)

Plasma PK Parameters	Dose Exploration Phase		Expanded Phase
	100 Units/m^2 N = 4	134 Units/m^2 N = 5	100 Units/m^2 N = 18
Cytarabine			
Actual Dose (mg)	106 (113, 46.0-151)	155 (115, 77.7-279)	87.6 (65.5, 44.0-209)
AUC_{48h} (ng × h/mL)	2237575 (43.4)	3127565 (32.7)	2178534 (39.0)
AUC_{0-48}/D (h*ng/mL/mg)	23134.0 (102.8)	23234.2 (80.1)	27828.1 (58.7)
AUC_{last} (ng × h/mL)	3049826 (48.5)	4225148 (41.5)	3049429 (47.7)
AUC_{last}/D (h*ng/mL/mg)	31531.8 (106.0)	31388.0 (79.7)	38952.7 (59.4)
AUC_{∞} (ng × h/mL)	3272299 (52.7)	4510790 (44.6)	3278296 (51.1)
AUC_{∞}/D (h*ng/mL/mg)	33831.9 (107.3)	33510.0 (79.0)	41876.2 (59.4)
C_{max} (ng/mL)	91607 (31.7)	117609 (19.7)	82803 (20.4)
C_{max}/D (ng/mL/mg)	947.1 (94.3)	873.7 (77.3)	1057.7 (60.0)
t_{max} (h)	1.73 (1.68, 2.08)	1.97 (1.50, 5.17)	2.00 (1.50, 12.02)
$t_{½}$ (h)	28.5 (28.5)	28.6 (19.2)	29.4 (27.9)
CL (mL/h)	43.2 (102.8)	43.0 (80.1)	35.9 (58.7)
V_{ss} (mL)	1736 (105.1)	1679 (89.5)	1501 (69.3)
Molar Ratio C:D AUC_{48h}	7.95 (37.2)	7.03 (23.3)	5.96 (10.7)
Molar Ratio C:D AUC_{last}	8.57 (37.1)	7.59 (27.5)	6.36 (12.5)
Molar Ratio C:D AUC_{∞}	7.26 (3.2)	7.81 (29.8)	6.50 (13.7)
Daunorubicin			
Actual Dose (mg)	46.4 (49.5, 20.2-66.4)	68.4 (50.7, 34.2-123)	38.5 (28.8, 19.4-92.0)
AUC_{48h} (ng × h/mL)	610702 (41.5)	965409 (30.1)	792767 (38.6)
AUC_{0-48}/D (h*ng/mL/mg)	14350.0 (107.0)	16299.7 (71.6)	23015.1 (60.3)
AUC_{last} (ng × h/mL)	771934 (41.6)	1206643 (38.1)	1040673 (44.6)
AUC_{last}/D (h*ng/mL/mg)	18138.5 (109.0)	20372.7 (72.1)	30212.1 (60.4)
AUC_{∞} (ng × h/mL)	847450 (49.2)	1252827 (38.8)	1093606 (46.7)
AUC_{∞}/D (h*ng/mL/mg)	21397.0 (138.4)	21152.4 (71.8)	31748.8 (60.8)
C_{max} (ng/mL)	39086 (29.1)	47891 (12.7)	36420 (23.1)
C_{max}/D (ng/mL/mg)	918.4 (93.6)	808.6 (71.4)	1057.3 (62.5)
tmax (h)	1.69 (1.58, 1.75)	1.60 (1.50, 2.00)	1.83 (1.50, 2.05)
t½ (h)	21.1 (13.2)c	25.8 (8.6)	26.3 (22.2)
CL (mL/h)	69.7 (107.0)	61.4 (71.6)	43.4 (60.3)
Vss (mL)	1594 (102.4)c	1806 (78.5)	1504 (66.7)

During the Dose Exploration Phase after the day 5 infusion, the geometric mean (geomean) molar ratio of cytarabine:daunorubicin (C:D) AUC_{0-48} for the 100 units/m^2 dose was 7.95 (CV 37.2%). A similar value was observed for the 134 units/m^2 dose (7.03; CV 23.3%). GeoMean molar ratios for AUC_{0-48} were slightly lower, and closer to the expected 5:1 C:D ratio, during the Expanded Phase for the 100 units/m^2 dose (5.96; CV 10.7%).

Study AAML1421

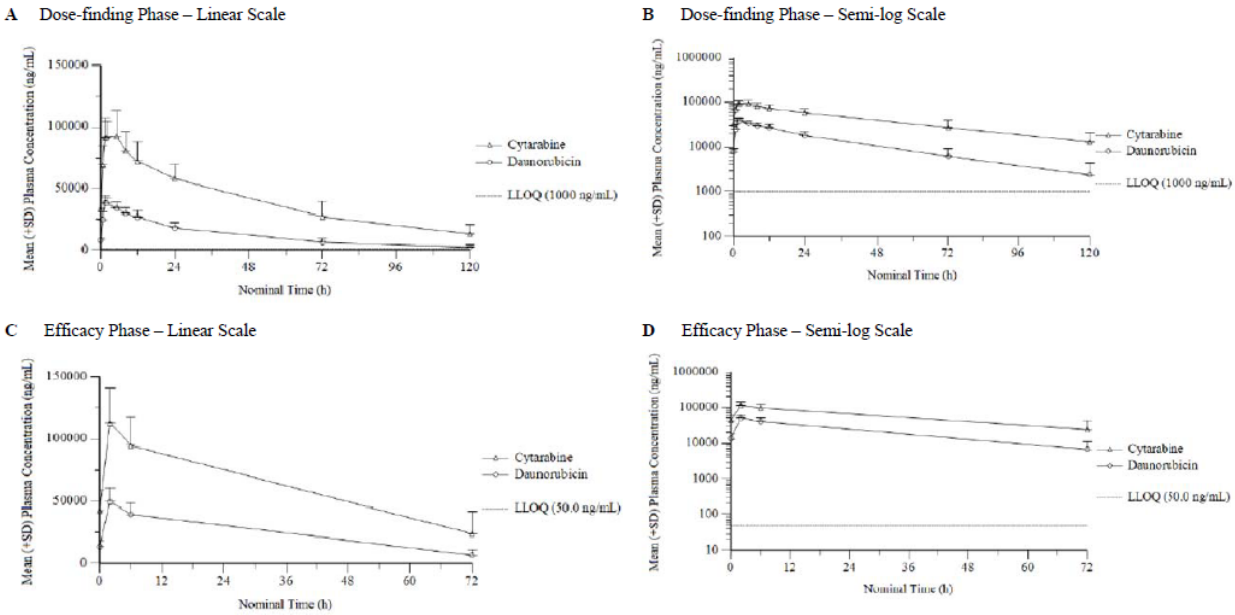
This study comprised 2 phases: Dose-finding Phase (n=6) and an Efficacy Phase (total n=32). All patients received a dose of 135 units/m^2 CPX-351.

Frequent plasma PK samples were collected in the Dose-finding Phase at the following times: Day 5: pre-dose, and 45 minutes, 90 minutes, 2, 5, 8, 12, 24, 72 and 120 hours after the start of the infusion. For one subject (#861842, the dose record was not consistent with treatment plan and other treatment record and the data were excluded from PK summary statistics.

Sparse plasma PK samples were collected in the Efficacy Phase in 22 patients at the following times: Cycle 1, Day 1: 2 hours after the start of the infusion; Day 5: pre-dose, 2 and 6 hours and 72 hours (± 24 hours) after the start of the Day 5 infusion.

The observed PK data are summarized in **Figure 2** and **Table 4**.

Figure 2. Mean (+SD) Plasma Concentrations of Cytarabine and Daunorubicin vs. Time Following a 90 Minute IV Infusion of 135 units/m2 CPX-351 – Day 5 of Dose-finding Phase and Efficacy Phase (Study AAML1421)



Notes: Open triangles represent mean plasma concentrations for cytarabine. Open circles represent mean plasma concentrations for daunorubicin.

Table 4. Geometric Mean (Geo Mean CV%) Plasma PK Parameters of Cytarabine and Daunorubicin Following a 90-Minute IV Infusion of 135 units/m^2 CPX-351 (Study AAML1421, Dose-finding Phase)

PK Parameter	Cytarabine (N = 5)	Daunorubicin (N = 5)
Actual Dose (units/m^2)[a]	135 (135, 134 – 137)	135 (135, 134 – 137)
Actual Dose (mg)[a]	220 (218, 122 – 370)	96.9 (95.9, 53.7 – 163)
AUC_{0-48} (ng*h/mL)	2848294 (24.1)	949730 (22.7)
AUC_{last} (ng*h/mL)	4418582 (34.8)	1288010 (35.3)
C_{max} (ng/mL)	94598 (18.3)	38890 (12.9)
t_{max} (h) [b]	5.00 (1.92 - 5.07)	2.00 (1.42 - 2.07)
$t_{1/2}$ (h)	41.1 (28.7)	28.8 (27.6)
CL (mL/h)	71.8 (65.2)	94.7 (65.2)
Vss (mL)	4158 (41.5)	3828 (45.9)

AUC_{0-48} = AUC from time 0 to 48 hours; **AUC_{last}** = AUC from time 0 to the last measurable non-zero concentration; **C_{max}** = maximum plasma concentration; **CL** = clearance; **Max** = maximum; **Min** = minimum; **$t_{1/2}$** = terminal half-life; **t_{max}** = time to maximum plasma concentration; **Vss** = volume of distribution at steady state.

[a] Mean (Median, Min – Max).

[b] Median (Min – Max),.

Note: 1 unit = 1 mg cytarabine and 0.44 mg daunorubicin.

1.5.3. Pharmacodynamics

The applicant did not submit any new data on pharmacodynamics.

1.5.4. PK/PD modelling

- **Population pharmacokinetic analysis**

Report JAZP-PMX-CPX351-1032_PPK: *Population PK Analysis of CPX-351 (Liposomal Cytarabine and Daunorubicin) in Children, Adolescents and Young Adults with Recurrent or Refractory Hematologic Malignancies* (2020-Jul-14)

Objectives

The objective was 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 and assess sources of variability in exposure. The analysis was performed to support dosing in paediatric patients with AML.

The final population PK models were subsequently used for exposure response modelling.

Methods

The dataset included information from paediatric studies AAML1421 and CPX-MA-1201 and previously conducted adult studies 101, 206 and 301. Individual concentration values were excluded from the population PK analysis if the actual collection time was not available or was evidently inaccurate, if the value corresponded to measurable drug in a Day 1 pre-dose sample, or (in rare cases) if inclusion of the value prohibited the PK model from providing a covariance matrix. Plasma concentrations below the limit of quantification (BLQ) of the assay were flagged and set to missing. All concentrations excluded from the

PK analysis were retained in the dataset and reasons for the exclusions were documented. Concentration data were log-transformed before the population PK analysis.

Prior cytarabine and daunorubicin population PK models developed for adult patients with hematologic malignancies were used as initial models; the models were developed using data from studies 101, 206 and 301.

The prior model for cytarabine was a 2-compartment model, with an OMEGA block on CL and central volume of distribution (Vc), a residual error model (log additive with ETA), and an allometric model of BSA on CL, Vc, peripheral clearance (Q), and peripheral volume of distribution (Vp). The CL, Vc, and Vp were mainly dependent upon BSA. The effect of bilirubin on CL was statistically significant, but the relationship was shallow, with an exponent of 0.197. Dose, formulation, and other intrinsic covariates did not exert a significant effect on the PK parameters.

The prior model for daunorubicin was a 2-compartment model, with an OMEGA block on PK parameters (CL, Vc, Q, and Vp), a residual error model (log additive with ETA); and an allometric model of BSA on CL, Vc, Q, and Vp was previously used to assess the concentration-time profiles of daunorubicin in adult patients with hematologic malignancies. The CL, Vc, and Vp of daunorubicin were mainly dependent upon BSA. The model also included an effect of bilirubin on CL and formulation (frozen) effect on all PK parameters (CL, Vc, Q, and Vp).

In the first step, data from the paediatric studies (CPX-MA-1201 and AAML142) were included in the dataset and population PK parameters were re-estimated using the prior models. In the second step, residual effects of age were explored (after taking into account differences in BSA by including BSA as a covariate for clearance and volume parameters) and the effect of age was formally evaluated within the models.

Modelling was performed using (FOCE and/or the mu-referencing method (SAEM/IMP methods with ITS pre-estimation if possible) in NONMEM (Version VII [Level 7.4]; ICON plc, Dublin, Ireland). Data set preparation, exploration, and visualization of the data will be performed using the statistical package in R (Version 3.5.2). Perl-Speak-NONMEM (PsN, Version 4.4.8) was used for modeling, stepwise analysis of covariates, and visual predictive checks (VPC).

Results

A total of 250 patients with AML were included in the analysis. The population included a total of 46 (18.4%) paediatric patients (1-17 years) and 204 (81.6%) adults (≥ 18 years). Overall, 22 (8.8%), 10 (4.0%) and 14 (5.6%) patients were in age category 1-5 years, 6-11 years and 12-17 years, respectively. The median age (range) in study CPX-MA-1201 and AAML1421 were 5.0 years (1 to 19 years) and 13.0 years (1 to 21 years), respectively. The median (range) BSA in study CPX-MA-1201 and AAML1421 were 0.74 m^2 (0.44 to 2.09 m^2) and 1.55 m^2 (0.45 to 2.75 m^2), respectively. Overall, the PK population included 148 (59.2%) male and 102 (40.8%) female patients, mainly of white origin (82.4%). All paediatric patients received the lyophilized formulation of CPX-351.

Cytarabine

Of 2614 samples assayed for cytarabine, a total of 2490 (95.3%) were included in the PK analysis. Most of the excluded samples (64; 2.4%) were BLQ first predose; only 19 (0.7%) were BLQ post dose.

The concentration-time profile of cytarabine declined in a bi-exponential manner. Using the previously developed model (run001), the PK parameters were robustly estimated with RSE values less than 20%. However, the goodness-of-fit (GOF) plots suggested that the population predictions (PRED) over-estimated the observed concentrations in children and young adults (CPX-MA-1201 and AAML1421) and under-estimated the observed concentrations in adults.

A covariate analysis was performed to assess the potential effects of age as categorical and continuous covariates. In addition, populations defined as children, adolescents and young adults (CPX-MA-1201 and AAML1421) vs adults were evaluated with and without age effects. Results of the covariate analysis are presented in **Table 5**. A model integrating the effect of populations (run003) defined as children, adolescents and young adults (CPX-MA-1201 and AAML1421) vs. adults (study 101, 206, and 301) resulted in the lowest reduction in objective function (ΔOFV = -21.3).

Table 5. Cytarabine - Covariate runs for age

Model	Covariate Effect	OFV	ΔOFV	Comment
run001	Original Model (Reference)	-4284.7929		
run002	Age on CL (power)	-4295.4323	-10.6	
run003	**Studies (CPX-MA-1201 and AAML1421) on CL and Vc**	**-4306.1193**	**-21.3**	**Best Model**
run004	Studies (CPX-MA-1201 and AAML1421) on CL and Vc; Age on CL (power)	-4307.7416	-22.9	95%CI for Age Effect includes 0
run005	Age Group (1-5, 6-11, 12-17 years) on CL	-4291.0174	-6.2	
run006	Pediatric (1-17 years) on CLand Vc	-4293.6333	-8.8	95%CI for Age Effect on CL includes 0

Typical population PK parameters of cytarabine derived with the final model are presented in **Table 6**. The population estimates of CL and Vc for cytarabine in adults were 0.101 L/h and 4.76 L, respectively. The population estimates of CL and Vc for cytarabine in children, adolescents and young adults were 0.0731 L/h and 3.91 L, respectively.

The population PK model included an allometric component that accounted for differences in BSA. The exponent for the effect of BSA on CL was 0.948 suggesting faster clearance in patients with higher BSA. For example, typical patients with BSA values of 0.44 and 2.8 m^2 (corresponding to the minimum and maximum in the population) would be expected to have CL values 75% lower and 44% higher, respectively (0.0252 and 0.146 L/h, respectively) relative to a typical subject with a BSA of 1.9 m^2 (0.101 L/h). These differences in CL are expected to be offset by the BSA-based dosing of CPX-351. For example, relative to the dose administered in a typical subject with a BSA of 1.9 m^2, doses administered to patients with BSA values of 0.44 and 2.8 m^2 would be 77% lower and 47% higher, respectively. As expected, BSA was identified as statistically significant covariates describing the variability of Vc.

Table 6. Final Population PK Parameters of Cytarabine (run003)

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 $(\exp(\omega^2)-1)^{0.5}$

GOF plots for the whole population indicated that the model structure of run003 was appropriate (**Figure 3**). A visual predictive check (VPC) of predicted vs. observed concentrations of cytarabine in children, adolescents and young adults (CPX-MA-1201 and AAML1421) and in adults are presented in **Figure 4**. Observed median and upper/lower 95th percentiles of cytarabine concentrations were contained within the model-predicted ranges, indicating that the model could reproduce the observed data.

Figure 3. Goodness-of-Fit plots for cytarabine (all studies; Final model (run003))

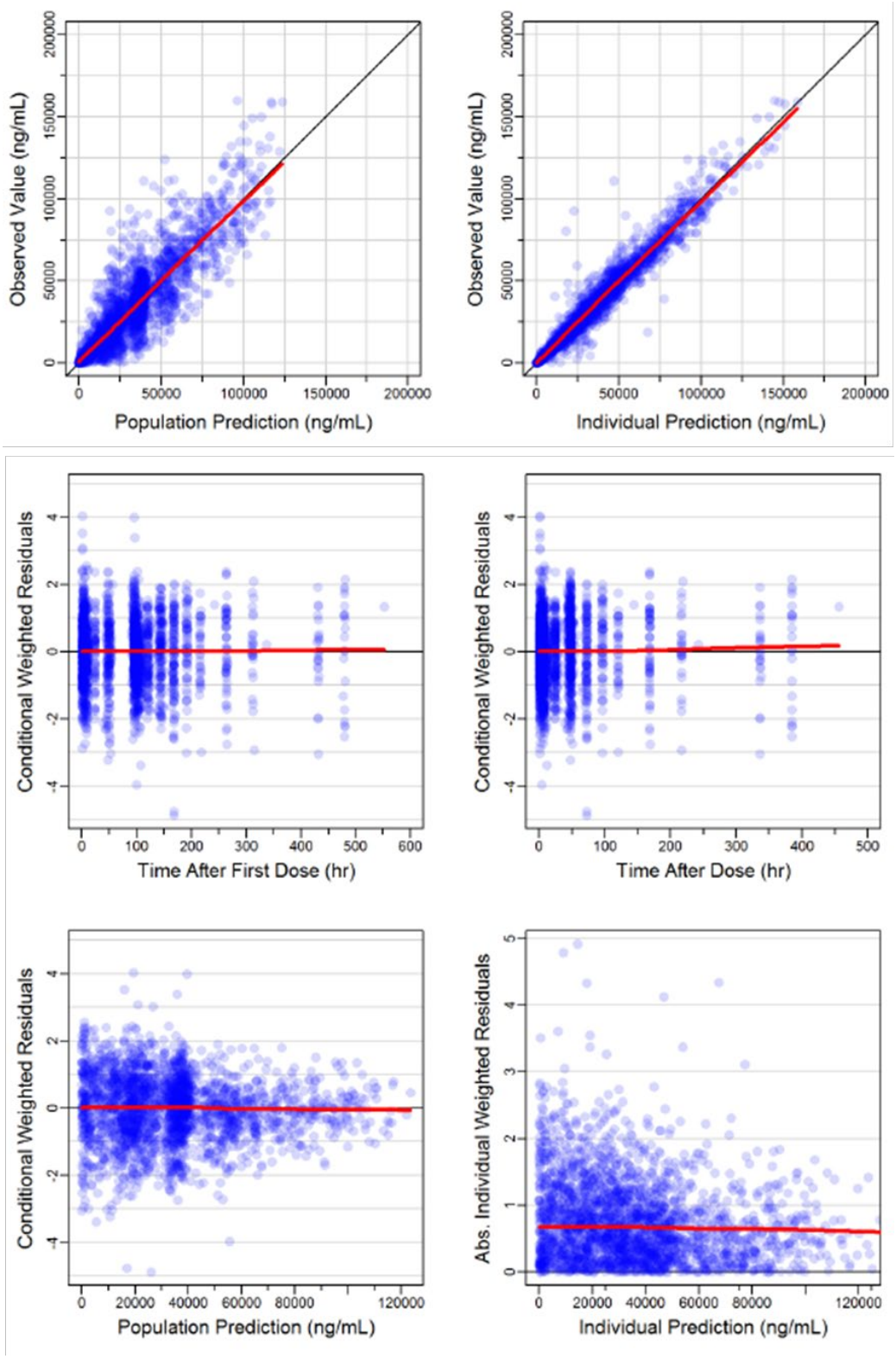
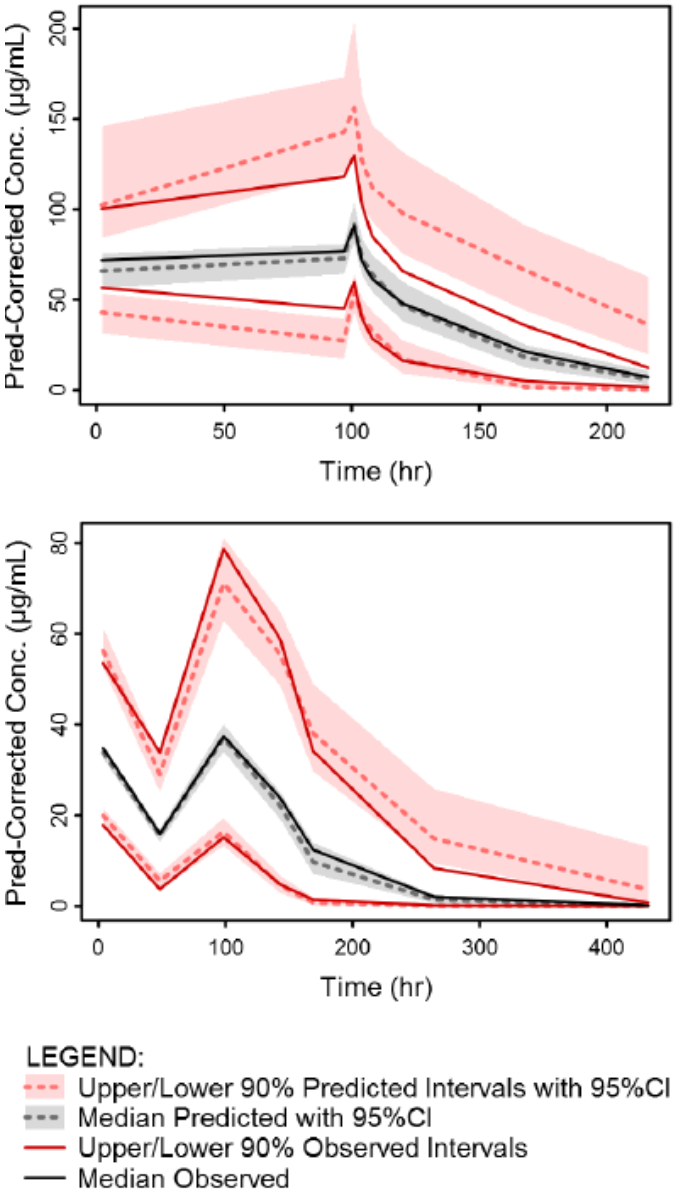


Figure 4. VPC for Final Model of Cytarabine (run003): Children, Adolescents and Young Adults (Top) and Adults (Bottom).



Daunorubicin

Of 2613 samples assayed for daunorubicin, a total of 2469 (94.5%) were included in the PK analysis. Most of the excluded samples (63; 2.4%) were BLQ first predose; only 39 (1.5%) were BLQ post dose.

The concentration-time profile of daunorubicin declined in a bi-exponential manner. The population PK model previously developed in adults (run001) was used in a first step to assess the concentration-time profiles in this expanded dataset. Population PK parameters were robustly estimated with RSE values less than 20%. However, the GOF plots suggested that the population predictions (PRED) over-estimated the observed concentrations in children, adolescents and young adults (CPX-MA-1201 and AAML1421) and under-estimated the observed concentrations in adults.

A covariate analysis was performed to assess the potential effects of age as categorical and continuous covariates. In addition, populations defined as children, adolescents and young adults (CPX-MA-1201 and

AAML1421) vs adults were evaluated with and without age effects. Results of the covariate analysis are presented in **Table 7**. A model integrating the effect of populations (run003) defined as children, adolescents and young adults (CPX-MA-1201 and AAML1421) vs. adults (study 101, 206, and 301) resulted in the lowest reduction in objective function (ΔOFV = -11.2).

Table 7. Daunorubicin - Covariate runs for age

Model	Covariate Effect	OFV	ΔOFV	Comment
run001	Original Model (Reference)	-4423.5646		
run002	Age on CL (power)	-4420.4856	3.1	95% CI for Age Effect includes 0
run003	**Studies (CPX-MA-1201 and AAML1421) on CL and Vc**	**-4434.8061**	**-11.2**	**Best Model**
run004	Studies (CPX-MA-1201 and AAML1421) on CL and Vc; Age on CL (power)	-4436.7695	-13.2	95% CI for Age Effect includes 0
run005	Age Group (1-5, 6-11, 12-17 years) on CL	-4419.2330	4.3	95% CI for Age Effect includes 0
run006	Pediatric (1-17 years) on CLand Vc	-4424.0089	-0.4	95% CI for Age Effect on CL includes 0

Typical population PK parameters of daunorubicin derived with the final model are presented in **Table 8**. The population estimates of CL and Vc for daunorubicin in adults were 0.140 L/h and 4.04 L, respectively. The population estimates of CL and Vc for daunorubicin in children, adolescents and young adults were 0.0932 L/h and 3.28 L, respectively.

The population PK model included an allometric component that accounted for differences in BSA. The exponent for the effect of BSA was 0.876 suggesting faster clearance in patients with higher BSA. For example, CL values in typical patients with BSA values of 0.44 and 2.8 m^2 (corresponding to the minimum and maximum in the population) would be expected to have CL values 72% lower and 40% higher (0.0389 and 0.197 L/h, respectively) than a typical subject with a BSA of 1.90 m^2 (0.140 L/h). These differences in CL are expected to be largely offset by BSA-based dosing of CPX-351. For example, relative to the dose administered to a typical subject with a BSA of 1.9 m^2, doses administered to patients with BSA values of 0.44 and 2.8 m^2 would be expected to be 77% lower and 47% higher, respectively. In addition, bilirubin and formulation (frozen vs lyophilized) remained statistically significant covariates on the CL of daunorubicin. Patients treated with the frozen formulation that was used in early studies would be expected to display a 18% lower CL relative to the current lyophilized formulation that was used in the pediatric studies. BSA was identified as statistically significant covariate describing the variability of Vc, as expected.

Table 8. Final Population PK Parameters of Daunorubicin (run003)

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		$CL = tvCL \cdot \exp(\eta CL)$
BSA_CL		0.876	0.103	11.7%	0.675 - 1.08		$\times (BSA/1.9)^{BSA\_CL}$
Bili_CL		0.155	0.0513	33.0%	0.0548 - 0.256		$\times (Bilirubin/0.6)^{Bili\_CL}$ if bilirubin is available*
Form_CL		-0.199	0.0829	41.7%	-0.361 - -0.0364		× exp(Form_CL) if Frozen 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		$Vc = tvVc \cdot \exp(\eta Vc)$
BSA_Vc		1.23	0.0584	4.7%	1.12 - 1.35		$\times (BSA/1.9)^{BSA\_Vc}$
Form_Vc		-0.167	0.0388	23.2%	-0.243 - -0.0912		× exp(Form_Vc) if Frozen 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		$Q = tvQ \cdot \exp(\eta Q)$
BSA_Q		1.00	fixed				$\times (BSA/1.9)^{BSA\_Q}$
Form_Q		-1.21	0.586	48.3%	-2.36 - -0.0650		× exp(Form_Q) if Frozen Formulation
Vp	L	0.788	0.173	22.0%	0.449 - 1.13		$Vp = tvVp \cdot \exp(\eta Vp)$
BSA_Vp		1.00	fixed	-	-		$\times (BSA/1.9)^{BSA\_Vp}$
Form_Vp		-1.49	0.376	25.2%	-2.23 - -0.756		× exp(Form_Vp) if Frozen Formulation
LogErr		0.141	0.00799	5.7%	0.125 - 0.157	13.2%	$\ln(Cobs) = \ln(Cpred) + LogErr \cdot \exp(\eta LogErr)$
BSV_CL		0.200(47.1%)	0.0208	10.4%	0.159 - 0.241	3.2%	$\omega^2 CL$
BSV_Vc		0.0372(19.5%)	0.00440	11.8%	0.0286 - 0.0458	10.3%	$\omega^2 Vc$
BSV_Q		1.80(224.7%)	0.298	16.5%	1.22 - 2.38	30.2%	$\omega^2 Q$
BSV_Vp		1.62(201.8%)	0.367	22.6%	0.903 - 2.34	28.8%	$\omega^2 Vp$
BSV_LogErr		0.392(69.3%)	0.0501	12.8%	0.294 - 0.491	17.9%	$\omega^2 LogErr$

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

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

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

Vp = peripheral volume of distribution; BSA_Vp = BSA effect on Vp; Form_Vp = formulation effect (Frozen) 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 $(\exp(\omega^2)-1)^{0.5}$

GOF plots for the whole population indicated that the model structure of run003 was appropriate **(Figure 5**). A visual predictive check (VPC) of predicted vs. observed concentrations of cytarabine in children, adolescents and young adults (CPX-MA-1201 and AAML1421) and in adults are presented in **Figure 6**. Observed median and upper/lower 95th percentiles of cytarabine concentrations were contained within the model-predicted ranges, indicating that the model could reproduce the observed data.

Figure 5. Goodness-of-Fit plots for daunorubicin (all studies; Final model (run003))

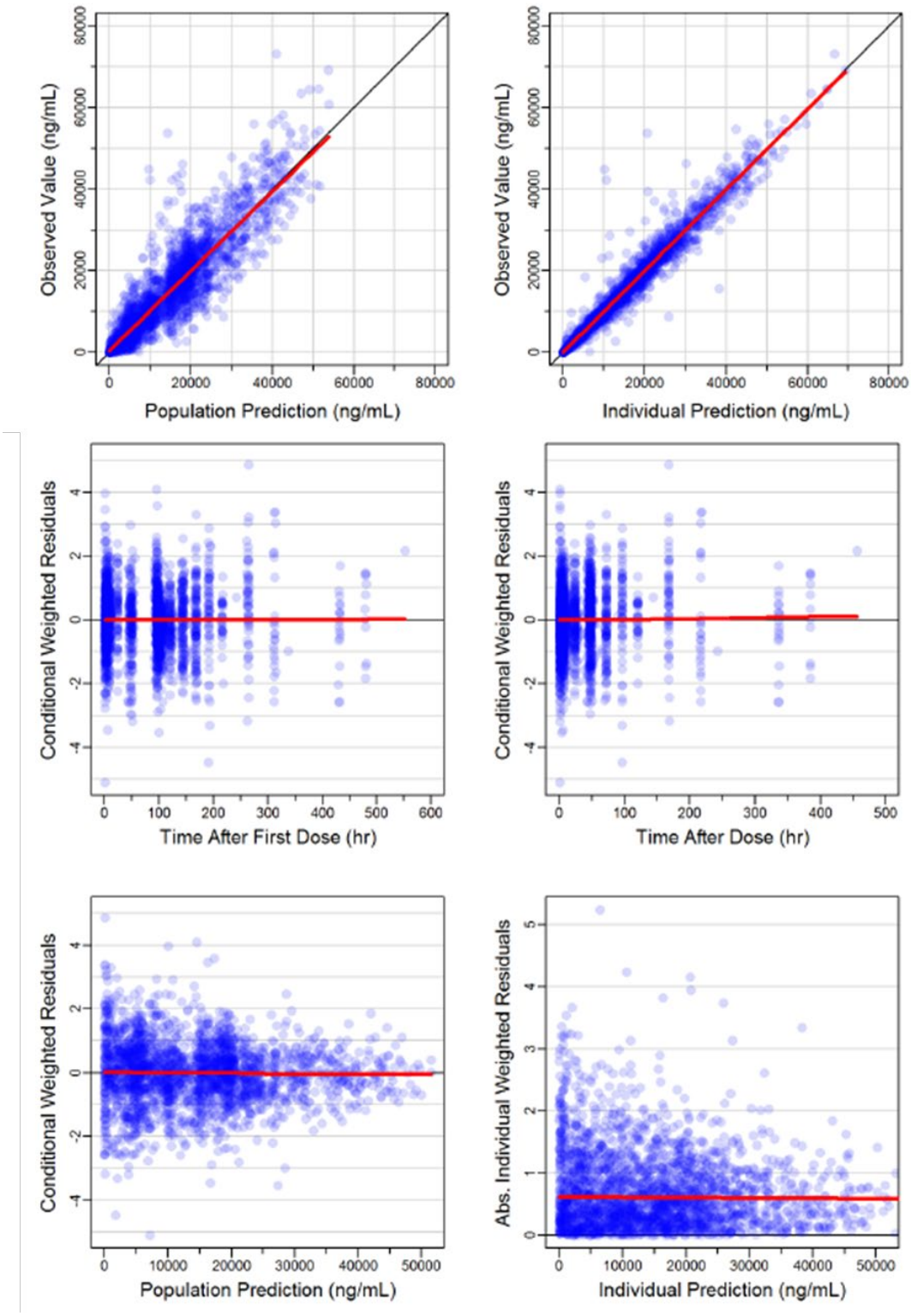
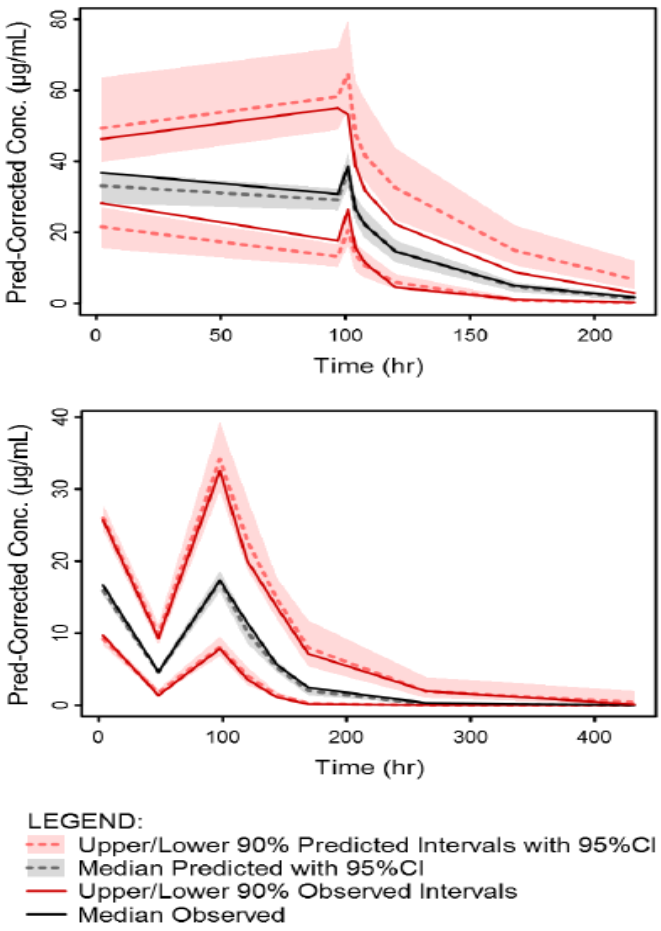


Figure 6: VPC for Final Model of Daunorubicin (run003): Children, Adolescents and Young Adults (Top) and Adults (Bottom).



Predicted exposures

The final population PK models were used to derive post hoc estimates for PK parameters, simulated dense concentration-time profiles and exposure parameters for cytarabine (**Table 9**) and daunorubicin (**Table 10**).

The predicted exposure parameters (C_{max}; AUC over 48 hours (AUC_{0-48}); concentration at 48 hours after the dose (C_{48})) were highly correlated, especially AUC_{0-48} and C_{48} but also C_{max} and the other two parameters.

Table 9. Cytarabine Predicted PK and Exposure Parameters by Age Group

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	V_c (L)	Q (L/h)	V_P (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
1 to 5 years (135 Units/m²)	N	22	22	22	22	22	22	22	22
	Mean (CV%)	0.0275 (51.6%)	0.946 (38.6%)	0.000557 (20.4%)	0.0421 (20.4%)	0.988 (37.7%)	2767 (33.5%)	102 (28.6%)	29.0 (42.4%)
	SD	0.0142	0.365	0.000113	0.00858	0.373	928	29.1	12.3
	GeoMean (CV%)	0.0247 (47.5%)	0.888 (36.6%)	0.000547 (19.4%)	0.0413 (19.4%)	0.930 (35.7%)	2601 (39.3%)	97.6 (30.3%)	25.6 (63.9%)
	Median	0.0248	0.848	0.000539	0.0407	0.888	2686	98.9	28.9
	Range	0.0145 to 0.0658	0.503 to 1.98	0.000409 to 0.000836	0.0309 to 0.0632	0.535 to 2.04	940 to 4516	52.2 to 161	4.04 to 51.6
	95% CI	0.0215 to 0.0334	0.794 to 1.10	0.000509 to 0.000604	0.0385 to 0.0457	0.832 to 1.14	2379 to 3154	89.5 to 114	23.9 to 34.2
6 to 11 years (135 Units/m²)	N	10	10	10	10	10	10	10	10
	Mean (CV%)	0.0447 (22.3%)	2.09 (33.9%)	0.00100 (16.0%)	0.0757 (16.0%)	2.17 (33.2%)	2783 (17.1%)	93.1 (15.7%)	33.5 (27.5%)
	SD	0.00995	0.709	0.000160	0.0121	0.719	475	14.6	9.19
	GeoMean (CV%)	0.0438 (20.5%)	2.01 (30.2%)	0.000990 (15.4%)	0.0749 (15.4%)	2.08 (29.5%)	2740 (19.6%)	92.0 (17.3%)	32.3 (30.3%)
	Median	0.0420	1.99	0.000980	0.0741	2.05	2856	97.8	32.4
	Range	0.0322 to 0.0688	1.36 to 3.86	0.000817 to 0.00136	0.0618 to 0.102	1.43 to 3.96	1701 to 3325	62.5 to 109	17.6 to 47.7
	95% CI	0.0385 to 0.0509	1.65 to 2.53	0.000902 to 0.00110	0.0682 to 0.0832	1.72 to 2.61	2489 to 3078	84.1 to 102	27.8 to 39.2

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	V_c (L)	Q (L/h)	V_P (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
12 to 17 years (135 Units/m²)	N	14	14	14	14	14	14	14	14
	Mean (CV%)	0.0815 (46.0%)	3.36 (26.2%)	0.00158 (14.5%)	0.119 (14.5%)	3.48 (25.7%)	2806 (34.9%)	94.3 (26.4%)	33.8 (50.2%)
	SD	0.0375	0.879	0.000229	0.0173	0.892	979	24.9	17.0
	GeoMean (CV%)	0.0741 (47.7%)	3.24 (28.4%)	0.00156 (14.7%)	0.118 (14.7%)	3.36 (27.8%)	2644 (37.8%)	91.1 (28.5%)	29.7 (59.2%)
	Median	0.0727	3.52	0.00156	0.118	3.65	2610	94.1	31.3
	Range	0.0338 to 0.162	1.85 to 4.91	0.00123 to 0.00193	0.0927 to 0.146	1.94 to 5.04	1309 to 4428	51.1 to 140	11.6 to 65.3
	95% CI	0.0619 to 0.101	2.90 to 3.82	0.00146 to 0.00170	0.110 to 0.128	3.01 to 3.94	2293 to 3319	81.3 to 107	24.9 to 42.7
≥ 18 years (135 Units/m²)	N	9	9	9	9	9	9	9	9
	Mean (CV%)	0.0707 (46.3%)	4.07 (28.2%)	0.00187 (17.6%)	0.141 (17.6%)	4.21 (27.7%)	3654 (29.9%)	109 (25.1%)	51.2 (37.3%)
	SD	0.0327	1.15	0.000329	0.0249	1.17	1093	27.3	19.1
	GeoMean (CV%)	0.0653 (42.0%)	3.94 (27.2%)	0.00184 (17.0%)	0.139 (17.0%)	4.08 (26.7%)	3502 (32.3%)	106 (25.2%)	47.6 (44.0%)
	Median	0.0591	3.99	0.00192	0.145	4.13	3742	106	55.6
	Range	0.0404 to 0.140	2.61 to 6.47	0.00148 to 0.00255	0.112 to 0.193	2.74 to 6.67	2156 to 5185	76.8 to 152	23.4 to 73.9
	95% CI	0.0493 to 0.0920	3.32 to 4.82	0.00165 to 0.00208	0.125 to 0.157	3.45 to 4.97	2940 to 4368	91.2 to 127	38.7 to 63.6

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	V_c (L)	Q (L/h)	V_p (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
Adults (Study 206, and Study 301) (100 Units/m²)	N	156	156	156	156	156	156	156	156
	Mean (CV%)	0.123 (66.0%)	5.07 (27.2%)	0.00181 (12.7%)	0.137 (12.7%)	5.20 (26.7%)	1928 (45.9%)	61.3 (31.6%)	25.5 (64.2%)
	SD	0.0810	1.38	0.000230	0.0174	1.39	884	19.4	16.3
	GeoMean (CV%)	0.103 (64.3%)	4.89 (27.5%)	0.00180 (12.8%)	0.136 (12.8%)	5.02 (26.9%)	1720 (53.6%)	58.3 (32.9%)	19.3 (105.0%)
	Median	0.104	4.82	0.00181	0.137	4.96	1764	59.0	22.0
	Range	0.0282 to 0.436	2.36 to 9.19	0.00123 to 0.00248	0.0927 to 0.187	2.46 to 9.36	410 to 4974	26.2 to 126	0.569 to 84.5
	95% CI	0.110 to 0.135	4.85 to 5.28	0.00178 to 0.00185	0.134 to 0.140	4.98 to 5.42	1789 to 2067	58.3 to 64.4	22.9 to 28.0

Abbreviations: AUC_{48h} = area under the concentration-time curve from time 0 to 48 on Day 5; C_{48} = concentration 48 hours after dosing on Day 5; CI = confidence interval; CL = clearance; C_{max} = maximum concentration on Day; CV% = coefficient of variation; GeoMean = geometric mean; Q = peripheral clearance; PK = Pharmacokinetic(s); SD = standard deviation; V_c = central volume of distribution; V_p = peripheral volume of distribution, V_{ss} = total volume of distribution.
Note: In the "Adult" group, 1 subject from Study 310-301 did not have dose on Day 5 and was excluded from the PK parameter calculations.

Table 10. Daunorubicin Predicted PK and Exposure Parameters by Age Group

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	Vc (L) Q (L/h)		Vp (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
1 to 5 years (135 Units/m²)	N	22	22	22	22	22	22	22	22
	Mean (CV%)	0.0364 (58.3%)	0.786 (32.1%)	0.0125 (59.7%)	0.277 (82.9%)	1.06 (42.1%)	967 (36.7%)	45.6 (26.2%)	8.17 (48.0%)
	SD	0.0212	0.252	0.00747	0.230	0.447	355	11.9	3.93
	GeoMean (CV%)	0.0318 (53.5%)	0.750 (32.2%)	0.0103 (76.7%)	0.203 (102.0%)	0.985 (40.8%)	898 (43.5%)	44.1 (27.3%)	6.93 (74.3%)
	Median	0.0288	0.720	0.0127	0.225	0.968	991	44.9	8.44
	Range	0.0181 to 0.0821	0.420 to 1.39	0.00246 to 0.0302	0.0323 to 0.982	0.543 to 2.16	352 to 1706	25.8 to 71.1	1.35 to 15.0
	95% CI	0.0275 to 0.0452	0.680 to 0.891	0.00939 to 0.0156	0.181 to 0.373	0.876 to 1.25	819 to 1116	40.6 to 50.6	6.53 to 9.81
6 to 11 years (135 Units/m²)	N	10	10	10	10	10	10	10	10
	Mean (CV%)	0.0645 (30.9%)	1.73 (29.1%)	0.0526 (88.5%)	0.963 (99.4%)	2.69 (48.9%)	896 (26.0%)	40.2 (19.2%)	8.67 (27.8%)
	SD	0.0200	0.504	0.0465	0.957	1.32	233	7.72	2.41
	GeoMean (CV%)	0.0621 (28.4%)	1.68 (25.5%)	0.0377 (104.0%)	0.655 (116.0%)	2.46 (44.1%)	864 (30.6%)	39.4 (20.9%)	8.3 (31.4%)
	Median	0.0580	1.49	0.0362	0.673	2.36	986	41.9	9.02
	Range	0.0449 to 0.107	1.35 to 2.97	0.0127 to 0.147	0.164 to 3.34	1.62 to 5.46	508 to 1146	27.6 to 48.7	4.75 to 11.9
	95% CI	0.0521 to 0.0769	1.42 to 2.04	0.0238 to 0.0815	0.369 to 1.56	1.88 to 3.51	752 to 1041	35.4 to 44.9	7.18 to 10.2

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	Vc (L) Q (L/h)		Vp (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
12 to 17 years (135 Units/m²)	N	14	14	14	14	14	14	14	14
	Mean (CV%)	0.103 (36.9%)	2.96 (26.0%)	0.0356 (64.3%)	0.472 (49.2%)	3.43 (24.5%)	982 (32.5%)	40.3 (22.9%)	9.70 (48.6%)
	SD	0.0378	0.769	0.0229	0.232	0.840	319	9.23	4.71
	GeoMean (CV%)	0.0960 (39.4%)	2.87 (26.9%)	0.0290 (83.4%)	0.414 (61.3%)	3.33 (26.2%)	930 (36.5%)	39.2 (25.3%)	8.53 (61.1%)
	Median	0.0955	2.97	0.0337	0.449	3.57	950	42.4	8.17
	Range	0.0477 to 0.167	1.83 to 4.45	0.00433 to 0.0983	0.112 to 0.930	1.94 to 5.10	406 to 1586	24.0 to 58.9	2.23 to 18.7
	95% CI	0.0827 to 0.122	2.56 to 3.36	0.0236 to 0.0476	0.350 to 0.594	2.99 to 3.87	815 to 1149	35.4 to 45.1	7.23 to 12.2
≥ 18 years (135 Units/m²)	N	9	9	9	9	9	9	9	9
	Mean (CV%)	0.0939 (48.9%)	3.34 (28.8%)	0.0603 (119.0%)	1.04 (94.7%)	4.38 (33.3%)	1275 (32.6%)	47.2 (24.9%)	14.8 (41.8%)
	SD	0.0459	0.961	0.0718	0.981	1.46	415	11.7	6.18
	GeoMean (CV%)	0.0864 (42.5%)	3.24 (25.5%)	0.0388 (116.0%)	0.741 (99.2%)	4.17 (33.8%)	1214 (35.0%)	46.0 (24.8%)	13.5 (51.9%)
	Median	0.0784	3.30	0.0306	0.652	3.95	1225	45.7	13.3
	Range	0.0568 to 0.193	2.45 to 5.65	0.0140 to 0.238	0.284 to 2.84	2.74 to 6.63	700 to 1923	33.9 to 67.6	5.60 to 22.4
	95% CI	0.0639 to 0.124	2.71 to 3.97	0.0134 to 0.107	0.395 to 1.68	3.42 to 5.33	1004 to 1547	39.5 to 54.9	10.8 to 18.8

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	Vc (L) Q (L/h)		Vp (L)	V_{ss} (L)	AUC_{48h} (µg × h/mL)	C_{max} (µg/mL)	C_{48} (µg/mL)
Adults (CLTR0310-206, and CLTR0310-301) (100 Units/m²)	N	156	156	156	156	156	156	156	156
	Mean (CV%)	0.164 (60.3%)	4.22 (25.2%)	0.130 (218.0%)	2.27 (180.0%)	6.49 (70.6%)	615 (41.8%)	25.8 (25.5%)	6.37 (59.2%)
	SD	0.0988	1.06	0.285	4.09	4.58	257	6.58	3.77
	GeoMean (CV%)	0.143 (54.2%)	4.09 (25.4%)	0.0543 (182.0%)	1.08 (151.0%)	5.65 (49.9%)	558 (49.5%)	24.9 (27.7%)	5.09 (86.6%)
	Median	0.142	4.11	0.0405	0.820	5.17	580	25.1	5.64
	Range	0.0590 to 0.557	2.07 to 7.94	0.00192 to 2.83	0.100 to 25.8	2.39 to 30.9	140 to 1213	11.8 to 41.4	0.278 to 16.1
	95% CI	0.148 to 0.179	4.05 to 4.38	0.0858 to 0.175	1.63 to 2.92	5.77 to 7.21	575 to 655	24.7 to 26.8	5.78 to 6.96

Abbreviations: AUC_{48h} = area under the curve from t = 0 to 48 hours postdose; C_{48} = concentration at 48 hours postdose; CI = confidence interval; CL = total body clearance of drug following vascular administration; C_{max} = maximum concentration; CV% = coefficient of variation for the arithmetic mean, expressed as a percentage; GeoMean = geometric mean; h = hour, N = number, or sample size; PK = pharmacokinetic(s); Q = distributional clearance; SD = standard deviation; Vc = central volume of distribution; Vp = peripheral volume of distribution; V_{ss} = steady-state volume of distribution.
Note: In the "Adult" group, 1 subject from Study 310-301 did not have dose on Day 5 and was excluded from the PK parameter calculations.

Age Group	Statistic	PK Parameters					Day 5 Exposure		
		CL (L/h)	Vc (L)	Q (L/h)	Vp (L)	Vss (L)	AUC_{0-48hr} (µg·h/mL)	C_{max} (µg/mL)	C_{48hr} (µg/mL)
Adults ≥18 years* (100 or 135 U/m²)	N	166	166	166	166	166	166	166	166
	Mean(CV%)	0.160(61.0%)	4.17(25.6%)	0.126(220.0%)	2.20(181.0%)	6.37(70.4%)	636(42.6%)	26.4(26.7%)	6.64(59.6%)
	SD	0.0976	1.07	0.277	3.98	4.48	271	7.06	3.96
	GeoMean(CV%)	0.139(54.9%)	4.04(25.8%)	0.0531(177.0%)	1.06(147.0%)	5.55(49.5%)	575(50.1%)	25.4(28.5%)	5.31(86.7%)
	Median	0.139	4.04	0.0396	0.817	5.13	592	25.5	6.04
	Range	0.0568-0.557	2.07-7.94	0.00192-2.83	0.100-25.8	2.39-30.9	138-1466	11.9-51.5	0.275-17.1
	95%CI	0.145-0.175	4.01-4.33	0.0839-0.168	1.59-2.80	5.68-7.05	594-677	25.3-27.5	6.04-7.24

CL = clearance; Vc = central volume of distribution; Q = peripheral clearance; Vp = peripheral volume of distribution, Vss = total volume of distribution; AUC_{0-48} = area under the concentration-time curve from time 0 to 48 on Day 5; C_{max} = maximum concentration on Day; C_{48} = concentration 48-h after dosing on Day 5; GeoMean = geometric mean, CV% = coefficient of variation.

NOTE: In the "Adult" group, one subject from Study 310-301 did not have dose on Day 5 and was excluded from the PK parameter calculations.

* Adults in study 310-206 (n=26) and 310-301 (n=131) received 100 U/m² while young adults in study CPX-MA-1201 (n=1) and AAML1421 (n=8) received 135 U/m².

- **Exposure-response analyses**

Pharmacometrics report: *Exposure-Response Analysis of CPX-351 (Liposomal Cytarabine and Daunorubicin) in Children, Adolescents and Young Adults with Recurrent or Refractory Hematologic Malignancies* (JAZP-PMX-CPX351-1032_ER; 14-Jul-2020)

The objective was to perform exposure-response (ER) analysis of key efficacy and safety endpoints in paediatric and young adult patients with AML treated with CPX-351.

Exposure-Response Analysis of Efficacy

Methods

The dataset was constructed by combining data from children, adolescents and young adults (Studies CPX-MA-1201 and AAML1421) and adult patients with relapsed and refractory AML (Studies 101 and 206). For Study 101, only therapeutic doses (i.e., approximately 100 and 134/135 units/m^2) were included in the analysis. The following exposure parameters of cytarabine and daunorubicin were derived based on a population PK model:

- Area under the curve up to 48 hours post dose on Day 5 Cycle 1 (AUC_{0-48})
- Maximum concentration on Day 5 Cycle 1 (C_{max})
- Concentration at 48 hours post dose on Day 5 Cycle 1 (C_{48})

In addition, the observed predose concentration on Day 5, Cycle 1 ($C_{predose}$) was also considered in the ER analysis.

Exposure parameters were merged with the following response endpoints (see Table 5.3.4.5):

- Complete response (CR)
- CR + CRp (complete response with partial recovery of platelet count)
- CR + CRp + CRi (complete response with partial recovery of platelet count and incomplete blood count recovery)

The following covariates were tested in efficacy analyses.

- Age, as
    - continuous parameter (years)
    - categorical (pediatric vs. adults): 1-17 vs. ≥18 years
    - categorical (pediatric vs. young adults, adults and elderly): 18 to 29, 30 to < 60, and ≥60 years
- Sex (categorical, male, female)
- Bone marrow blast count (%) (categorical, <5% vs. 5-25% vs. > 25% blast count)
- White blood cell (WBC) count (x 10^9/L)
- Platelet count (x 10^9/L)

Table 11. Definition of efficacy response criteria in each study

Definition	Study			
	305-101	**310-206**	**CPX-MA-1201**	**AAML1421**
Complete Response (CR)	- BMC <5%, - ANC ≥ 1000/µL, - Platelet ≥ 100,000/µL; - No Auer rods	- BMC <5%, - ANC ≥ 1000/µL, - Platelet ≥ 100,000/µL, - No Auer rods.	- BMC <5%, - ANC ≥ 1000/µL, - Platelet ≥ 100,000/µL;	- BMC <5%, - ANC ≥ 1000/µL, - Platelet ≥ 100,000/µL;
Complete Response with Partial Recovery of Platelet Count (CRp)	Not Monitored	Not Monitored	- BMC <5%, - ANC ≥ 1000/µL, - No platelet transfusions	- BMC <5%, - ANC ≥ 1000/µL, - No platelet transfusions
Complete Response with Incomplete Blood Count Recovery (CRi)	Not Monitored	- BMC <5%, - ANC < 1000/µL, - Platelet < 100,000/µL, - No Auer rods	- BMC <5%, - ANC < 1000/µL, - Platelet < 100,000/µL;	- BMC <5%, - ANC < 1000/µL, - Platelet < 100,000/µL;
Partial Response (PR)	- Presence of Auer rods and BMC <5%, OR - Presence of Auer rods and BMC 5% to 25%	Not Monitored	- BMC 5% to 25%	- BMC 5% to 25%

BMC = bone marrow blasts count; **ANC** = absolute neutrophil count

A logistic regression model was developed to link cytarabine and/or daunorubicin exposures to response criteria. The model tested the effect of cytarabine and daunorubicin separately and for the combined effect assuming additive properties. Finally, the logistic regression model tested the combined effect of cytarabine and daunorubicin with an interaction term to potentially capture a less than or more than additive effect. The best fitting model according to Akaike information criterion (AIC) was selected.

The statistical significance of covariates was tested in the logistic regression models with a p-value of 0.05.

Data set preparation, exploration, visualization of the data and exposure-response analyses were performed using R (Version 3.5.2) with comprehensive R archive network (CRAN) and Certara Strategic Consulting (CSC) package.

Results

Dataset: Exposure-response analysis of efficacy was performed based on response criteria in children, adolescents and young adults (study CPX-MA-1201 and AAML1421) and adult patients with relapsed and refractory AML (study 101 and 206). A total of 81 patients were included in the analysis. The population included a total of 43 (53.1%) pediatric patients (1-17 years) and 38 (46.9%) adults (≥ 18 years). Baseline characteristics are summarized in **Table 12** and **Table 13**). Of the 81 patients included in the analysis, a total of 28 (30.9%) patients presented CR, 16 (24.6%) patients presented CRi and 1 (1.92%) patient presented CRp, while 39 (48.1%) presented a negative response (**Table 14**).

Table 12. Baseline Characteristics in the Exposure-Efficacy Population – Categorical Data

Covariate	Sub-Population	Study ID				Overall
		305-101	310-206	1201	1421	
Age Categories	1-5 years	-	-	16(64.0%)	6(22.2%)	22(27.2%)
	6-11 years	-	-	3(12.0%)	6(22.2%)	9(11.1%)
	12-17 years	-	-	5(20.0%)	7(25.9%)	12(14.8%)
	≥18 years	16(100.0%)	13(100.0%)	1(4.0%)	8(29.6%)	38(46.9%)
Age Groups	Pediatric (1-17 years)	-	-	24(96.0%)	19(70.4%)	43(53.1%)
	Adults (≥18 years)	16(100.0%)	13(100.0%)	1(4.0%)	8(29.6%)	38(46.9%)
Per Protocol Age Population	Children and Younger Adults	-	-	25(100.0%)	27(100.0%)	52(64.2%)
	Adults	16(100.0%)	13(100.0%)	-	-	29(35.8%)
Total Bilirubin Categories	Not Recorded	-	-	25(100.0%)	27(100.0%)	52(64.2%)
	<1.2 mg/dL	15(93.8%)	12(92.3%)	-	-	27(33.3%)
	1.2 - 3 mg/dL	1(6.3%)	1(7.7%)	-	-	2(2.5%)
Formulation	Frozen	16(100.0%)	-	-	-	16(19.8%)
	Lyophilized	-	13(100.0%)	25(100.0%)	27(100.0%)	65(80.2%)
Race	White	12(75.0%)	13(100.0%)	19(76.0%)	19(70.4%)	63(77.8%)
	Black	1(6.3%)	-	2(8.0%)	3(11.1%)	6(7.4%)
	Asian	3(18.8%)	-	-	1(3.7%)	4(4.9%)
	Other	-	-	-	2(7.4%)	2(2.5%)
	Unknown	-	-	4(16.0%)	2(7.4%)	6(7.4%)
Renal Function	Not Recorded	-	-	-	27(100.0%)	27(33.3%)
	CRCL ≥90 mL/min	5(31.3%)	6(46.2%)	18(72.0%)	-	29(35.8%)
	CRCL 60 to 89 mL/min	10(62.5%)	3(23.1%)	7(28.0%)	-	20(24.7%)
	CRCL 30 to 56 mL/min	1(6.3%)	4(30.8%)	-	-	5(6.2%)
	CRCL 15 to 29 mL/min	-	-	-	-	-
Sex	Male	11(68.8%)	7(53.8%)	13(52.0%)	15(55.6%)	46(56.8%)
	Female	5(31.3%)	6(46.2%)	12(48.0%)	12(44.4%)	35(43.2%)

CRCL= creatinine clearance

Table 13. Baseline Characteristics in the Exposure-Efficacy Population – Continuous Data

Covariate	Statistic	Study ID				Overall
		305-101	310-206	CPX-MA-1201	AAML1421	
Age (years)	n	16	13	25	27	81
	Mean (CV%)	59.8(20.4%)	63.8(17.2%)	6.3(93.7%)	11.6(56.6%)	27.9(96.2%)
	Median (Min-Max)	61.5(36-76)	63.0(37-80)	4.0(1-19)	13.0(1-21)	16.0(1-80)
BSA (m^2)	n	16	13	25	27	81
	Mean (CV%)	1.98(19.4%)	1.94(16.5%)	0.93(55.8%)	1.41(43.4%)	1.46(44.7%)
	Median (Min-Max)	1.90(1.44-2.8)	1.88(1.32-2.67)	0.69(0.44-2.09)	1.51(0.45-2.75)	1.64(0.44-2.8)
Body Weight (kg)	n	16	13	25	27	81
	Mean (CV%)	83.6(34.9%)	81.0(27.1%)	28.8(83.1%)	52.8(64.2%)	56.0(63.5%)
	Median (Min-Max)	75.1(49-156.5)	79.7(41.9-133.3)	16.8(9.1-90.4)	50.2(9.4-145.3)	59.4(9.1-156.5)
ALP (U/L)	n	16	13	-	-	29
	Mean (CV%)	111.3(59.7%)	91.6(43.8%)	-	-	102.5(54.8%)
	Median (Min-Max)	89.5(47-319)	72.0(54-164)	-	-	86.0(47-319)
ALT (U/L)	n	16	13	25	-	54
	Mean (CV%)	31.7(55.1%)	38(105.2%)	53.4(90%)	-	43.2(92.1%)
	Median (Min-Max)	24.0(15-77)	22.0(9-153)	40.0(22-219)	-	30.5(9-219)
AST (U/L)	n	16	13	-	-	29
	Mean (CV%)	27.7(57.2%)	24.8(41.8%)	-	-	26.4(51.2%)
	Median (Min-Max)	22.5(12-73)	23.0(9-40)	-	-	23.0(9-73)
Total Bilirubin (mg/dL)	n	16	13	-	-	29
	Mean (CV%)	0.70(50.8%)	0.56(53.7%)	-	-	0.64(52.4%)
	Median (Min-Max)	0.60(0.3-1.8)	0.50(0.2-1.2)	-	-	0.60(0.2-1.8)
Direct Bilirubin (mg/dL)	n	-	-	25	-	25
	Mean (CV%)	-	-	0.1(60.8%)	-	0.1(60.8%)
	Median (Min-Max)	-	-	0.1(0.1-0.4)	-	0.1(0.1-0.4)
Creatinine Clearance (mL/min)	n	16	13	25	-	54
	Mean (CV%)	86.0(33%)	101.5(56.1%)	120.7(34.8%)	-	105.8(42.2%)
	Median (Min-Max)	79.9(53.3-165.6)	88.0(42.3-211.7)	110.0(62.2-229.6)	-	93.2(42.3-229.6)
WBC (10^9/L)	n	16	13	25	26	80
	Mean (CV%)	7.0(168.5%)	12.8(233.4%)	10.7(191.9%)	9.1(150.5%)	9.8(192.1%)
	Median (Min-Max)	2.4(0.4-44.8)	3.8(0.7-110.9)	2.0(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, **WBC**= white blood cells.
Note: The WBC value for ID AAML1421-AL013-852842 (750 10^9/L) was excluded from descriptive statistics.

Table 14. Number and Percentage of Patients with Response

Study	Number Subject with Response / Total Subject Number (%) 95% CI (%)			
	Complete Response (CR)	**Complete Response with Incomplete Blood Count Recovery (CRi)**	**Complete Response with Partial Recovery of Platelet Count (CRp)**	**Negative Response**
305-101	8/16 (50.0%) (28.0, 72.0)	Not Monitored	Not Monitored	8/16 (50.0%) (46.4, 84.3)
310-206	2/13 (15.4%) (2.71, 46.3)	3/13 (23.1%) (6.16, 54.0)	Not Monitored	8/13 (61.5%) (32.3, 84.9)
CPX-MA-1201	5/25 (20.0%) (7.61, 41.3)	3/25 (12.0%) (3.15, 32.3)	0/25 (0%)	17/25 (68.0%) (46.4, 84.3)
AAML1421	10/27 (37.0%) (20.1, 57.5)	10/27 (37.0%) (20.1, 57.5)	1/27 (3.70%) (0.194, 20.9)	6/27 (22.2%) (9.38, 42.7)
Overall	28/81 (30.9%) (21.3, 42.2)	16/65 (24.6%) (15.1, 37.1)	1/52 (1.92%) (0.100, 11.6)	39/81 (48.1%) (37.0, 59.5)

Probability of (CR, CRi or CRp): CR, CRi and CRp were assessed in CPX-MA-1201 and AAML1421 (i.e., children, adolescents and young adults). In all, 29 of 52 patients were classified as responders (CR, CRi or CRp). Various exposure-response models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of response (**Table 15**). Cytarabine C_{48} was associated with the best statistical goodness-of-fit (AIC = 67.750) in the logistic regression model; the AIC value for daunorubicin C_{48} was similar (AIC = 67.950).

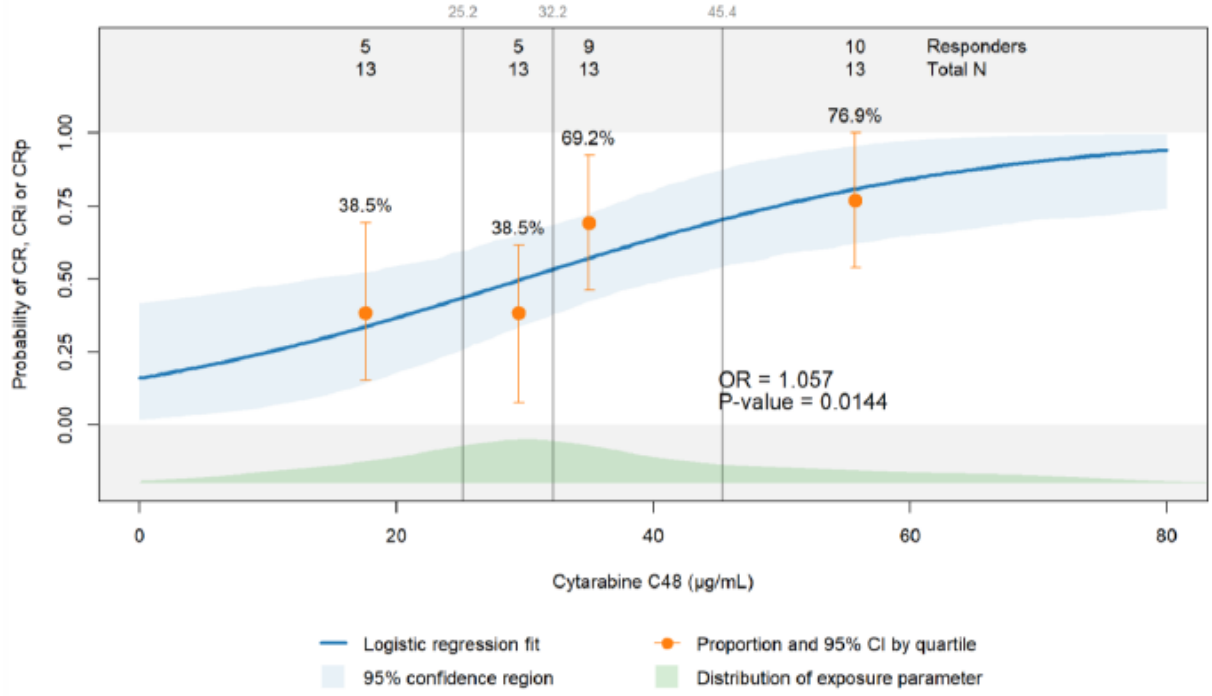
Table 15. Univariate Exposure-Response Analysis of Efficacy (Probability of CR, CRi or CRp)

Model	**Degrees of Freedom**	**AIC**	**BIC**	**Statistical Significance of Exposure (p<0.05)**
Model 1: Daunorubicin AUC0-48	2	70.16931	74.07179	Yes
Model 2: Daunorubicin Cmax	2	72.60428	76.50676	No
Model 3: Daunorubicin C48	2	67.94995	71.85244	Yes
Model 4: Cytarabine AUC0-48	2	70.30395	74.20644	Yes
Model 5: Cytarabine Cmax	2	73.62035	77.52283	No
Model 6: Cytarabine C48	2	**67.74995**	**71.65243**	**Yes**
Model 7: Daunorubicin C48 + Cytarabine C48	3	69.4637	75.31743	No
Model 8: Interaction between Daunorubicin C48 and Cytarabine C48	4	70.19235	77.99732	No

Note: Studies CPX-MA-1201 and AAML1421 were included in the analysis.
All exposure parameters were derived using the population PK model.
AIC = Akaike information criterion; **AUC0-48** = area under the concentration-time curve from time zero to 48 h post-dose on Day 5 (Cycle 1); **BIC** = Bayesian information criterion; **C48** = Concentration 48-h after dosing on Day 5 (Cycle 1); **Cmax** = maximum concentration on Day 5 (Cycle 1).

The probability of response (CR, CRi or CRp) as a function of the C_{48} of cytarabine on Day 5 is presented in **Figure 7**. The effect of cytarabine exposure (C_{48}) on the probability of response was statistically significant (p=0.0144) with an odds ratio of 1.057. These results suggest that the odds of response increased by approximately 5.7% for each 1 unit increment of cytarabine C_{48} (i.e., 1 µg/mL).

Figure 7. Probability of Response (CR, CRi or CRp) as a Function of Cytarabine C_{48}



Subsequently, multivariate regression analyses were performed to identify potential factors affecting the probability of response (in addition to cytarabine C_{48}). None of the tested covariates (age, sex, bone marrow blast count, WBC count, platelet count, haemoglobin) explained the variability in response. Parameters derived with the final exposure-response model of cytarabine C_{48} on the probability of response (CR, CRi or CRp) are presented in **Table 16**.

Table 16. Exposure-Response Parameters: Impact of Cytarabine C_{48} on the Probability of Response (CR, CRi or CRp)

Term	Parameter Estimates (95% CI)	(P-Value)
Intercept	-1.653 (-3.367, -0.178)	0.0388
Slope of Drug Effect (cytarabine C48)	0.0555 (0.0151, 0.106)	0.0144
C48 = concentration 48-h after dosing on Day 5 (Cycle 1)		

The impact of cytarabine C_{48} (after converting from the logit scale) on the probability of response (CR, CRi or CRp) are presented below:

- The estimated odds of response without cytarabine (C_{48} = 0 µg/mL) was 0.191 (i.e., exp[- 1.653]), suggesting a 16.1% probability of response (odds/1+odds).
- The estimated odds of response for a 20 µg/mL increment in C_{48} (0.0555 x 20 = 1.11) was 3.03 (i.e., exp[1.11]). The odds for the combined intercept and drug effect (C_{48} = 20 µg/mL) is 0.581 (i.e., exp[-1.653 + 1.11]) which corresponds to a 36.7% probability of response.
- The estimated odds of response for a 40 µg/mL increment in C_{48} (0.05550 x 40 = 2.22) was 9.21 (i.e., exp[2.22]). The odds for the combined intercept and drug effect (C_{48} = 40 µg/mL) is 1.76 (i.e., exp[-1.653 + 2.22]) which corresponds to a 63.8% probability of response.

For both cytarabine and daunorubicin, model-predicted C_{48} and AUC_{0-48} were highly correlated with each other and both predicted parameters were highly correlated with the observed Day 5 predose concentration ($C_{predose}$) as well (r=0.88 to r=0.95 for each comparison). Daunorubicin C_{48} and cytarabine and daunorubicin AUC_{0-48} and $C_{predose}$ were statistically significant predictors of response (CR, CRi or CRp).

Probability of (CR or CRp): CR and CRp were assessed in Studies CPX-MA-1201 and AAML1421. In all, 16 of 52 patients were classified as responders (CR or CRp). Various exposure-response models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of response (CR or CRp) obtained in pediatric studies (Studies CPX-MA-1201 and AAML1421). None of the exposure parameters of cytarabine or daunorubicin were statistically significantly associated with the probability of response (CR or CRp).

Probability of (CR or Cri): CR and CRi were assessed in Studies CPX-MA-1201, AAML1421 and 310-206. In all, 33 of 65 patients were classified as responders (CR or Cri). Various exposure-response models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of response (**Table 17**).

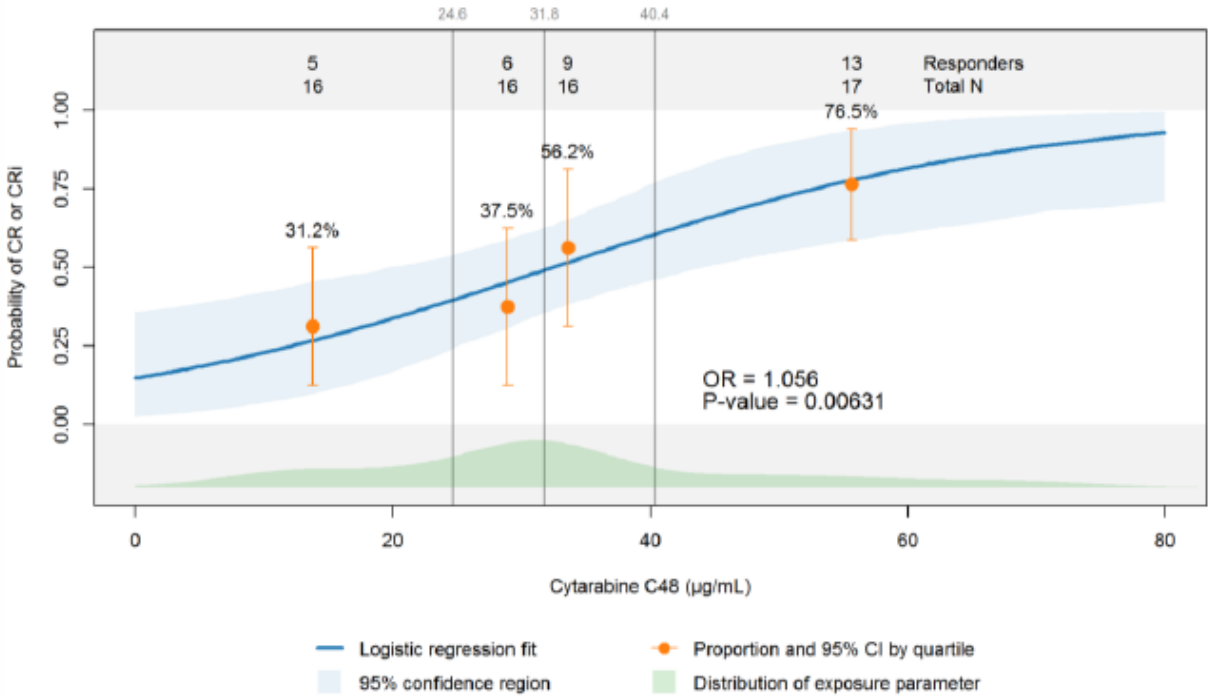
Table 17. Univariate Exposure-Response Analysis of Efficacy (Probability of CR or Cri)

Model	Degrees of Freedom	AIC	BIC	Statistical Significance of Exposure (p<0.05)
Model 1: Daunorubicin AUC0-48	2	85.06764	89.41641	Yes
Model 2: Daunorubicin Cmax	2	89.08843	93.43720	Yes
Model 3: Daunorubicin C48	2	**81.89673**	**86.24551**	**Yes**
Model 4: Cytarabine AUC0-48	2	86.57304	90.92182	Yes
Model 5: Cytarabine Cmax	2	89.95635	94.30513	No
Model 6: Cytarabine C48	2	**84.72990**	**89.07867**	**Yes**
Model 7: Daunorubicin C48 + Cytarabine C48	3	83.78283	90.30599	No
Model 8: Interaction between Daunorubicin C48 and Cytarabine C48	4	84.36424	93.06179	No

Note: Studies CPX-MA-1201, AAML1421 and 310-206 were included in the analysis.
All exposure parameters were derived using the population PK model.
AIC = Akaike information criterion; **AUC0-48** = area under the concentration-time curve from time zero to 48 h post-dose on Day 5 (Cycle 1); **BIC** = Bayesian information criterion; **C48** = Concentration 48-h after dosing on Day 5 (Cycle 1); **Cmax** = maximum concentration on Day 5 (Cycle 1).

The C_{48} of cytarabine and daunorubicin were associated with the best statistical goodness-of-fit (AIC of 69.544 and 68.681, respectively). Cytarabine C_{48} was selected for subsequent analyses for consistency with other analyses. The probability of response (CR or CRi) as a function of cytarabine C_{48} on Day 5 is presented in **Figure 8**. The effect of cytarabine exposure (C_{48}) on the probability of response (CR or CRi) was statistically significant (p=0.00631) with an odds ratio of 1.056. These results suggest that the odds of response increased by approximately 5.6% for each 1 unit increment of cytarabine C_{48} (i.e., 1 µg/mL).

Figure 8. Probability of Response (CR or CRi) as a Function of Cytarabine C_{48}



Subsequently, multivariate regression analyses were performed to identify potential factors affecting the probability of response (in addition to cytarabine C_{48}). None of the tested covariates (age, sex, bone marrow blast count, WBC count, platelet count, haemoglobin) explained the variability in response. Parameters derived with the final exposure-response model of cytarabine C_{48} on the probability of response (CR, CRi or CRp) are presented in **Table 18**.

Table 18. Exposure-Response Parameters: Impact of Cytarabine C_{48} on the Probability of Response (CR or CRi)

Term	Parameter Estimates (95% CI)	(P-Value)
Intercept	-1.749 (-3.218, -0.475)	0.0113
Slope of Drug Effect (cytarabine C48)	0.0540 (0.0183, 0.0971)	0.00631
C48 = concentration 48-h after dosing on Day 5 (Cycle 1)		

The impact of cytarabine C_{48} (after converting from the logit scale) on the probability of response (CR or CRi) are presented below.

- The estimated odds of response without cytarabine exposure (C_{48} = 0 µg/mL) was 0.174 (i.e., exp[-1.7494]), suggesting a 14.8% probability of response (odds/1+odds).
- The estimated odds of response for a 20 µg/mL increment in C_{48} (0.0540x 20 = 1.08) was 2.94 (i.e., exp[1.08]). The odds for the combined intercept and drug effect (C_{48} = 20 µg/mL) is therefore 0.512 (i.e., exp[-1.174 + 1.08]) which corresponds to a 33.9% probability of response.
- The estimated odds of response for a 40 µg/mL increment in C_{48} (0.00540 x 40 = 2.16) was 8.67 (i.e., exp[2.16]). The odds for the combined intercept and drug effect (C_{48} = 40 µg/mL) is 1.51 (i.e., exp[-1.174+ 2.16]) and a 60.1% probability of response.

Probability of (CR): Various exposure-response models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of response (CR) obtained in in all studies (Studies CPX-MA-1201, AAML1421, 310-206 and 310-101). In all, 28 of 81 patients were classified as responders (CR). None of the exposure parameters of cytarabine or daunorubicin were statistically significantly associated with the probability of response (CR).

Exposure-response analyses for safety

Methods

Exposure-response analysis of safety was performed based on data collected in all studies (0305-101, 310-206, 310-301, CPX-MA-1201 and AAML1421). The exposure-safety population included patients with at least 1 measurable concentration of cytarabine and daunorubicin on Day 5, Cycle 1.

In a first step, treatment emergent adverse events (TEAE) were merged with C_{max} and classified according to the quartile of exposure for the overall safety population and for only pediatric patients in the safety population. Descriptive statistics were derived according to the following toxicity grade and severity.

- Adverse events grades (grades 1, 2, 3, 4 and 5 according to NCI-CTC toxicity grade)
- Adverse events grade ≥3 (according to NCI-CTC toxicity grade)
- Serious treatment-emergent adverse events (SAE)

Then, descriptive statistics were derived for adverse events (AEs) according to the "body system or organ class" (AEBODSYS, e.g., blood and lymphatic system disorders) and "dictionary derived" terms (AEDECOD, e.g., febrile neutropenia). Only AEs associated with a "definite" or "possible" causality with CPX-351 were included in the analysis. Based on the descriptive statistics results, key AEs were selected for a formal exposure-response analysis. Predicted exposure parameters of cytarabine and daunorubicin (AUC_{0-48}, C_{max} or C_{48} on Day 5, Cycle 1) were merged with AEs of interest.

Logistic regression models were developed to link cytarabine and/or daunorubicin exposures to the above probability of AEs.

Results

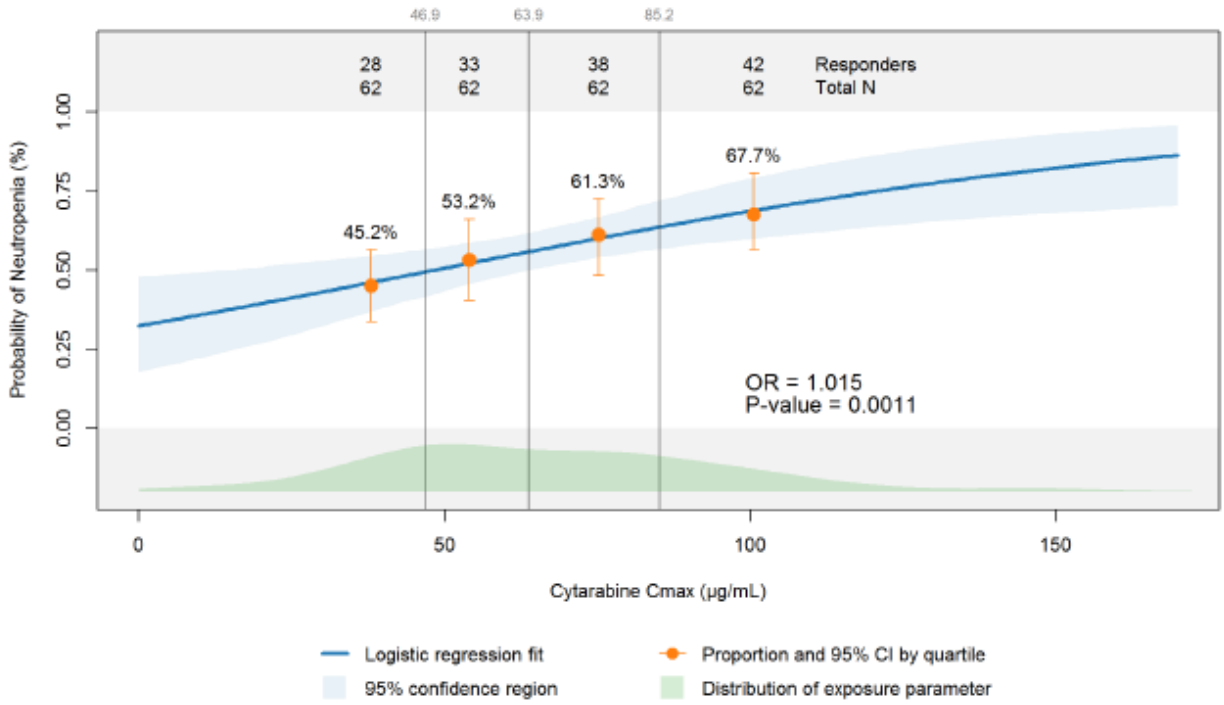
The exposure-safety population included a total of 46 (18.5%) pediatric patients (1-17 years) and 204 (81.5%) adults (≥ 18 years). The population included 147 (59.3%) male and 101 (40.7%) female patients, mainly of white origin (82.3%). The Phase III study (310-301) contributed the largest number of patients in the exposure-safety population (130 patients; 52.4%).

Of a total of 178 patients who presented an adverse event associated with the "blood and lymphatic system disorders" preferred term, 141 (79.2%) presented neutropenia. Of a total of 203 patients who presented an adverse event associated with the "skin and subcutaneous tissue disorders" preferred term, 79 (38.9%) presented a rash. Based on the above, exposure-response analyses were performed to determine the impact of drug exposure on the probability of neutropenia or rash.

Neutropenia

Various ER models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of neutropenia. Of all models tested, the C_{max} of cytarabine and AUC of daunorubicin were associated with the best statistical goodness-of-fit (AIC = 332.057 and 332.522, respectively). The C_{max} of cytarabine was used in subsequent analyses for consistency with analyses for rash (see below). The probability of neutropenia as a function of the C_{max} of cytarabine on Day 5 is presented in **Figure 9**.

Figure 9. Probability of Neutropenia as a Function of Cytarabine C_{max} on Day 5



The effect of cytarabine C_{max} on the probability of neutropenia was statistically significant (p=0.0011) with an odds ratio of 1.015. These results suggest that the odds of response increased by approximately 1.5% for each 1 unit increment of cytarabine C_{max} (i.e., 1 µg/mL).

A covariate analysis was performed to identify potential risk factors for the probability of neutropenia. After taking into account drug exposure in the logistic regression model, no tested covariate (age, sex, bone marrow blast count, WBC count, platelet count) explained the probability of neutropenia.

Parameters derived with the final exposure-response model of cytarabine C_{max} on the probability of neutropenia are presented in **Table 19**.

Table 19. ER Parameters: Impact of Cytarabine C_{max} on the Probability of Neutropenia

Term	Parameter Estimates (95% CI)	(P-Value)
Intercept	-0.730 (-1.415, -0.0696)	0.0327
Slope of Drug Effect (C_{max} of cytarabine)	0.0152 (0.00592, 0.0250)	<0.01

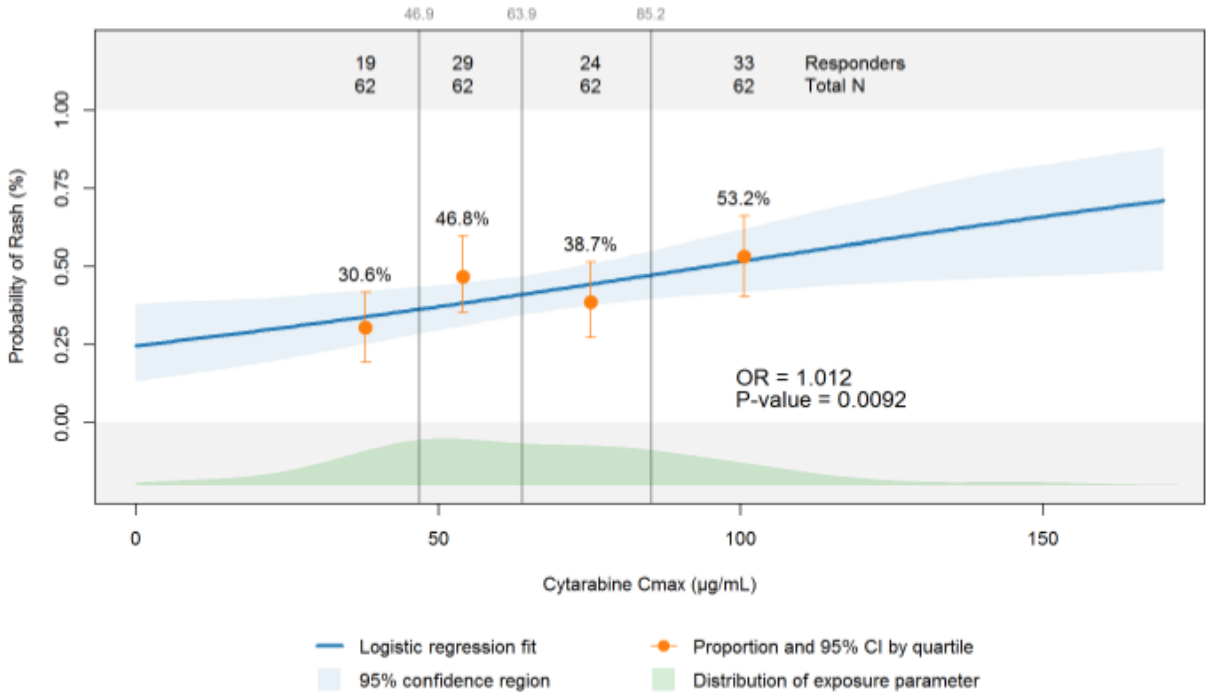
The magnitude of effects of cytarabine C_{max} (after converting from the logit scale) are presented below.

- The estimated odds of neutropenia without cytarabine exposure (C_{max} = 0 µg/mL) was 0.482 (i.e., exp[-0.730]), suggesting a 32.5% probability of neutropenia (odds/1+odds).
- The odds for a 50 µg/mL increment in C_{max} (0.0152 x 50 = 0.760) was 2.14 (i.e., exp[0.760]). The odds for the combined intercept and drug effect (C_{max} = 50 µg/mL) is 1.03 (i.e., exp[-0.730 + 0.759]) which corresponds to a 50.7% probability of neutropenia
- The odds for a 100 µg/mL increment in C_{max} (0.0152 x 100 = 1.52) was 4.57 (i.e., exp[1.52]). The odds for the combined intercept and drug effect (C_{max} = 100 µg/mL) is 2.20 (i.e., exp[-0.730 + 1.52]) which corresponds to a 68.8% probability of neutropenia

Rash

Various ER models were developed to assess the effect of cytarabine and/or daunorubicin exposures on the probability of a rash event. Of all models tested, the C_{max} of cytarabine was associated with the best statistical goodness-of-fit based on the AIC values. The probability of rash as a function of the C_{max} of cytarabine on Day 5 is presented in **Figure 10**.

Figure 10. Probability of rash as a function of cytarabine C_{max}



The effect of cytarabine C_{max} on the probability of rash was statistically significant (p=0.0092) with an odds ratio of 1.012. These results suggest that the odds of a rash increased by approximately 1.2% for each 1 unit increment of C_{max} (i.e., 1 µg/mL).

A covariate analysis was performed to identify potential risk factors for the probability of rash. After taking into account drug exposure in the logistic regression model, no tested covariate (age, sex, bone marrow blast count, WBC count, platelet count) explained the probability of rash. Parameters derived with the final exposure-response model of cytarabine C_{max} for the probability of rash are presented in **Table 20**.

Table 20. ER Parameters: Impact of Cytarabine C_{max} on the Probability of Rash

Term	Parameter Estimates (95% CI)	(P-Value)
Intercept	-1.11 (-1.797, -0.453)	<0.01
Slope: Cytarabine Cmax (µg/mL)	0.0118 (0.00289, 0.0211)	0.0106

The impact of cytarabine C_{max} (after converting from the logit scale) on the probability of rash are presented below.

- The estimated odds of rash without cytarabine exposure (C_{max} = 0 ng/mL) was 0.330 (i.e., exp[-1.11]), suggesting a 24.8% probability of rash (odds/1+odds).

- The odds for a 50 µg/mL increment in C_{max} (0.0118 x 50 = 0.590) was 1.80 (i.e., exp[0.590]). The odds for the combined intercept and drug effect (C_{max} = 50 µg/mL) is 0.595 (i.e., exp[-0.845 + 0.590]) which corresponds to a 37.3% probability of rash
- The odds for a 100 µg/mL increment in C_{max} (0.0118 x 100 = 1.18) was 3.25 (i.e., exp[1.18]). The odds for the combined intercept and drug effect (C_{max} = 100 µg/mL) is 1.07 (i.e., exp[-1.11 + 1.18]) which corresponds to a 51.7% probability of rash

Time to neutrophil recovery and platelet recovery

Longitudinal measures of absolute neutrophil count (ANC) and platelet count were available in study CPX-MA-1201 and AAML1421 (total N=51). No statistically significant effect of cytarabine C_{max} was observed on the time to recovery of ANC or platelet count. Results should be interpreted with caution due to the low number of patients.

Distribution of TEAEs by exposure

The distribution of TEAEs across quartiles of cytarabine C_{max} for all studies are presented in **Table 21**. A gradual increase in frequency of Grade 3 to 5 TEAEs was observed across quartiles of cytarabine C_{max}. The probabilities of Grade 3 to 5 TEAEs for the 1st, 2nd, 3rd, and 4th quartiles of cytarabine C_{max} were 11.3%, 13.1%, 18.0% and 53.2%, respectively. The frequency of severe adverse events was low (n=11) with apparent gradual increases in frequencies across quartiles of exposure. Similar results were observed for daunorubicin C_{max}.

Table 21. Overall Summary of Treatment Emergent Adverse Events by Quartiles of Cytarabine C_{max} (All Studies)

	Cytarabine Quartiles of Cmax (µg/mL)				Overall (N=246)
	Q1 = [2.21,46.9) (N=62)	Q2 = [46.9,63.4) (N=61)	Q3 = [63.4,84.9) (N=61)	Q4 = [84.9,161] (N=62)	
Any TEAEs	62 (100%)	61 (100%)	61 (100%)	62 (100%)	246 (100%)
TEAEs by Maximum NCI-CTC Grade					
1	41 (66.1%)	34 (55.7%)	30 (49.2%)	18 (29.0%)	123 (50.0%)
2	14 (22.6%)	19 (31.1%)	20 (32.8%)	11 (17.7%)	64 (26.0%)
3	6 (9.7%)	7 (11.5%)	10 (16.4%)	28 (45.2%)	51 (20.7%)
4	1 (1.6%)	1 (1.6%)	1 (1.6%)	4 (6.5%)	7 (2.8%)
5	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)	1 (0.4%)
3-5	7 (11.3%)	8 (13.1%)	11 (18.0%)	33 (53.2%)	59 (24.0%)
TEAEs by Closest Relationship					
Not related	37 (59.7%)	32 (52.5%)	28 (45.9%)	34 (54.8%)	131 (53.3%)
Related	25 (40.3%)	29 (47.5%)	33 (54.1%)	28 (45.2%)	115 (46.7%)
Not severe	62 (100%)	60 (98.4%)	58 (95.1%)	55 (88.7%)	235 (95.5%)
Severe	0 (0%)	1 (1.6%)	3 (4.9%)	7 (11.3%)	11 (4.5%)

NCI-CTC= National Cancer Institute – comment toxicity criteria; **TEAE**= Treatment emergent adverse events
Note: Two patients did not have TEAEs. Only one TEAE for the higher NCI-CTC grade was retained by subject

In studies CPX-MA-1201 and AAML1421 (total N=53), probabilities of Grade 3 to 5 TEAEs for the 1st, 2nd, 3rd, and 4th quartiles of cytarabine C_{max} were 76.9%, 84.6%, 84.6% and 71.4%, respectively (**Table 22**). Similar results were observed daunorubicin C_{max}. Overall no apparent ER relationship of TEAEs was observed in study CPX-MA-1201 and AAML1421.

Table 22. Overall Summary of Treatment Emergent Adverse Events by Quartiles of Cytarabine C_{max} (Studies CPX-MA-1201 and AAML1421)

	Cytarabine Quartiles of Cmax (µg/mL)				
	Q1 = [51.1, 82.8) (N=13)	**Q2 = [82.8, 98.6) (N=13)**	**Q3 = [98.6, 111) (N=13)**	**Q4 = [111,161] (N=14)**	**Overall (N=53)**
Any TEAEs	13 (100%)	13 (100%)	13 (100%)	14 (100%)	53 (100%)
TEAEs by Maximum NCI-CTC Grade					
1	0 (0%)	0 (0%)	1 (7.7%)	4 (28.6%)	5 (9.4%)
2	3 (23.1%)	2 (15.4%)	1 (7.7%)	0 (0%)	6 (11.3%)
3	8 (61.5%)	9 (69.2%)	9 (69.2%)	9 (64.3%)	35 (66.0%)
4	2 (15.4%)	2 (15.4%)	1 (7.7%)	1 (7.1%)	6 (11.3%)
5	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	1 (1.9%)
3-5	10 (76.9%)	11 (84.6%)	11 (84.6%)	10 (71.4%)	42 (79.2%)
TEAEs by Closest Relationship					
Not related	3 (23.1%)	2 (15.4%)	7 (53.8%)	7 (50.0%)	19 (35.8%)
Related	10 (76.9%)	11 (84.6%)	6 (46.2%)	7 (50.0%)	34 (64.2%)
Not severe	12 (92.3%)	9 (69.2%)	11 (84.6%)	12 (85.7%)	44 (83.0%)
Severe	1 (7.7%)	4 (30.8%)	2 (15.4%)	2 (14.3%)	9 (17.0%)

NCI-CTC= National Cancer Institute – comment toxicity criteria; **TEAE**= Treatment emergent adverse events
Note: Two patients did not have TEAEs. Only one TEAE for the higher NCI-CTC grade was retained by subject

1.5.5. Discussion on clinical pharmacology

Two investigator-sponsored paediatric studies (CPX-MA-1201 and AAML1421) have been conducted in paediatric and young adult patients from 1 to 21 years of age with r/r AML. The studies were conducted independently and without input on design of the MAH.

Observed PK

Frequent plasma PK samples following the Day 5 dose were collected in 27 and in 5 paediatric and young adult patients in studies CPX-MA-1201 and AAML1421, respectively. In addition, sparse PK samples were available for 22 subjects in study AAML1421. The observed exposure (AUC over 48 hours following the Day 5 dose) in paediatric patients following intravenous doses 100 and 135 units/m^2 was approximately comparable to the exposure observed previously in adult patients at similar dose levels. This is expected, because the dose is adjusted by body surface area. Moreover, when cytarabine and daunorubicin are administered as components of Vyxeos liposomal, the liposomes govern their disposition kinetics: the volume of distribution is close to the blood volume and the rate of drug release from the liposomes becomes the factor that determines the rate of elimination.

No major deviations from dose proportionality were observed over the dose range 100 to 135 units/m^2 in the paediatric studies, which is in line with previous data in adult patients.

Population PK analyses

Population PK (PPK) analyses were conducted in accordance with pre-specified pharmacometric analysis plan. The analysis plan was included in the dossier, which is appreciated.

PPK analyses were conducted using previously developed adult PPK models for cytarabine and daunorubicin as the starting point. The proportion of paediatric subjects in the updated dataset was moderate (46/250 subjects; 18.4%). After the PPK parameters were re-estimated, the effects of age on PK parameters were further investigated. At this point, the PPK models over-estimated concentrations for paediatric studies (CPX-MA-1201 and AAML1421) population and under-estimated the concentrations in adult studies (101, 206 and 301) population. For both cytarabine and daunorubicin models, "paediatric study" categorical covariate effect on CL and Vc parameters improved the fits more than age-based covariates. The introduction of a study effect on paediatric studies led to lower estimates for CL and Vc. This effect appeared

to be only driven by the unexpectedly high exposure observed in young adults (18-21 years old) in studies CPX-MA-1201 and AAML1421.

One weakness of the PPK analysis is that serum bilirubin level data were not available for studies CPX-MA-1201 and AAML1421; bilirubin was a covariate for clearance for both cytarabine and daunorubicin in adult PPK models. It is acknowledged that the MAH does not have the data and the issue is not pursued; it is unlikely that the overall conclusions regarding the current variation application are affected by this lack of data given that the effect of bilirubin level on clearance was modest.

The MAH withdrew the application for the paediatric indication during the procedure. The responses to questions on PPK analyses were deemed sufficient for the final scope of the variation application. Simulations using the PPK models indicated that the predicted exposures following the Day 5 dose in patients 1-5, 6-11, and 12-17 years of age following the 135 units/m^2 dose were very similar, and approximately 40% higher than the exposure in adults (≥ 18 years of age) following the 100 units/m^2 dose, i.e. exposure increased by 40% for a 35% dose increase. However, the predicted exposures for young adults (18-21 years) from studies CPX-MA-1201 and AAML1421 were markedly higher compared with paediatric patients. As expected, the predicted exposure parameters (C_{max}; AUC over 48 hours (AUC_{0-48}); concentration at 48 hours after the dose (C_{48})) were highly correlated, especially AUC_{0-48} and C_{48} but also C_{max} and the other two parameters.

The MAH is reminded that because the final population PK models for cytarabine and daunorubicin have empirical covariate "paediatric study effect" on clearance and central volume parameters, use of the presented population PK models to predict PK in other populations is not recommended. The MAH should consider to re-develop the PPK models in future as more data become available; re-evaluation of the "formulation effect" on the PK of daunorubicin at that time is also recommended.

Exposure-response analyses

Exposure-response (ER) analyses for efficacy and safety were conducted in accordance with pre-specified pharmacometric analysis plan. The analysis plan was included in the dossier, which is appreciated.

ER analyses for efficacy were conducted for paediatric and adult patients with relapsed and refractory AML from studies CPX-MA-1201, AAML1421, 101 and 206. Various efficacy endpoints were tested. Because some endpoints were not monitored in the adult studies (101 and 206), the number of subjects in the efficacy ER analyses was variable.

For the strict [complete response (CR)] endpoint, no statistically significant association between predicted exposure and efficacy was observed; CR was observed in 28 of 81 (30.9%) patients. The least strict endpoint [CR, or response with incomplete blood count recovery (CRi), or response with partial recovery of platelet count (CRp)] was monitored only in the paediatric and young adult studies (CPX-MA-1201 and AAML1421). This joint endpoint was observed in 29 of 52 (55.8%) patients, and exposure to cytarabine or daunorubicin was a statistically significant predictor of response.

Of note, only dose levels 100-101 and 134-135 units/m^2 were investigated in the ER analyses for efficacy, and data for the higher dose are mainly from studies CPX-MA-1201 and AAML1421. Therefore, the sensitivity to detect exposure-efficacy relationships may be decreased when data from studies 101 and 206 are included in the analyses. On the other hand, the number of patients in studies CPX-MA-1201 and AAML1421 was relatively low (N=52), and the results should, therefore, be interpreted with caution.

A total of 250 patients, mostly (204/250) adults, were included in the ER analyses for safety. Treatment emergent adverse events (TEAEs) "neutropenia" and "rash" were frequently reported (in 79.2% and in 38.9% of patients, respectively) and were selected for ER analyses.

Probability of neutropenia increased approximately linearly with increasing predicted cytarabine (or daunorubicin) C_{max} and the association was statistically significant. The result is expected, because both

cytarabine and daunorubicin are known to cause bone marrow depression. Probability of rash also increased statistically significantly with increasing predicted cytarabine (or daunorubicin) C_{max}.

The probability of any TEAE of grade 3-5 increased with increasing predicted cytarabine (or daunorubicin) C_{max} in the overall safety population, whereas in the paediatric and young adult population (studies CPX-MA-1201 and AAML1421; N=53) this association was not observed. Because the number of paediatric and young adult patients was low, results for this subset should be interpreted with caution.

1.5.6. Conclusions on clinical pharmacology

A question on pharmacokinetics and exposure in young adult patients, which was initially raised as part of the MO on the proposed indication, as well as several other concerns on clinical pharmacology were not further pursued since MAH withdrew the application for the paediatric indication.

Information on paediatric PK will be added to section 5.2 of the SmPC within the current variation. See the annexed product information document for details.

1.6. Clinical efficacy

1.6.1. Dose response studies

Dose response in study CPX-MA-1201

Study Design

Study CPX-MA-1201 was a phase 1, single-center pilot study to assess the PK, toxicity and tolerability of CPX-351 in paediatric and young adult patients with relapsed / refractory hematologic malignancies. The primary efficacy objectives included determination of a safe and tolerable dose of CPX-351 (defined as maximum tolerated dose, MTD) that could be given to patients with advanced hematologic malignancies, recommended a dose of CPX-351 for future studies in young patients with previously untreated AML, and PK after CPX-351 administration to young patients with recurrent or refractory hematologic malignancies

The secondary efficacy objective of this study was to estimate the overall response rate (ORR) to a single course of CPX-351 to young patients with recurrent or refractory hematologic malignancies.

This study comprised 2 phases: a Dose Exploration Phase and an Expanded Phase.

The Dose Exploration Phase was used to determine a safe and tolerable dose of CPX-351 in patients between 1 and 21 years of age with hematologic malignancies in first or greater relapse or with disease refractory to standard induction chemotherapy. Two dose levels of CPX-351 were explored: 100 units/m2 administered intravenously (IV) once daily on Days 1, 3 and 5 (dose level 1), and 134 units/m2 IV once daily on Days 1, 3 and 5 (dose level 2). After completion of the Dose Exploration Phase, the Expanded Phase enrolled 3 to 18 patients between 1 and 30 years of age to collect additional toxicity / tolerability information and to estimate the ORR of CPX-351 using the dose determined during the Dose Exploration Phase.

At specific time points during the treatment course, all patients underwent PK assessments. Consenting patients also participated in a cardiotoxicity biomarker study.

Throughout the study, patients were monitored for safety and adverse events (AEs); documentation began from day 1 of study treatment and continued through the 30-day follow-up period after treatment was discontinued. Patients continued to be followed for 6 months after completing their treatment course.

Results

A total of 27 patients were enrolled in the study, received at least 1 dose of study drug, and comprised the safety population. A total of 9 patients were included in the Dose Exploration Phase. Of these, 5 patients received a dose of 134 units/m2 CPX-351 and 4 patients received a dose of 100 units/m2 CPX-351. All 9 patients (100.0%) completed course 1 of therapy and entered the follow-up period.

Among patients who received 134 units/m2 CPX-351, 4/5 (80.0%) patients completed the 6-month follow-up period, and 1/5 (20.0%) subject died during follow-up. Among patients who received 100 units/m2 CPX-351, 2/4 (50.0%) patients completed the 6-month follow-up period, and 2/4 (50.0%) patients died during follow-up.

A total of 18 patients were included in the Expanded Phase, and all received a dose of 100 units/m2 CPX-351. A total of 17/18 patients (94.4%) completed course 1 therapy and entered the follow-up period. One subject went off protocol therapy because of disease progression and pursuit of other therapy. A total of 11/18 (61.1%) patients completed the 6-month follow-up period, and 7/18 (38.9%) patients died during follow-up.

The majority of patients were white (77.8%) and there were slightly more female (51.9%) than male (48.1%) patients . Patients had a mean (SD) age of 6.7 (5.90) years, ranging from 1 to 19 years, with most patients (59.3%) in the age group 2 to < 12 years. No patients aged < 1 year were enrolled. The majority of patients enrolled had AML (23/27 patients, 85.2%) and 4/27 patients (14.8%) had ALL.

Maximum tolerated dose (MTD)

A minimum of 2 evaluable patients was entered at each dose level for determination of MTD. Once the MTD was defined, up to 3 to 18 additional patients were enrolled. The minimum number of patients required to determine a MTD was 5 patients; the maximum was 12.

During the Dose Exploration Phase, a rolling 6 trial design was employed. Two to 6 patients were concurrently enrolled onto a dose level, dependent upon 1) the number of patients enrolled at the current dose level, 2) the number of patients who experienced a dose-limiting toxicity (DLT) at the current dose level, and 3) the number of patients with tolerability data pending at the current dose level. Accrual was suspended when a cohort of 6 had enrolled or when the study endpoints were met.

Dose level assignment was based on the number of patients enrolled in the cohort at the time, the number of DLTs observed, and the number of patients at risk for developing a DLT.

The MTD of CPX-351 observed in adults with AML was 100 units/m2, and it was projected to be tolerable in children based upon previous experience with liposomal anthracycline preparations in pediatric patients. If the 100 units/m2 dose was tolerable, then patients were entered into the study at 134 units/m2. This dose was chosen since it would deliver a total daunorubicin dose of 177 mg/m2, which is comparable to the dose of liposomal daunorubicin administered with fludarabine and high-dose cytarabine by the AML-Berlin / Frankfurt/ Muenster (BFM) study group during re-induction therapy for children with relapsed AML (Sander 2010).

The 134 unit/m2 dose resulted in DLTs in 2 patients; therefore, the 100 unit/m2 dose was administered to all patients in the Expansion Phase.

D*ose* response in study AAML1421

Study AAML1421 was a phase 1/2, multicenter study of CPX-351 for children with AML in first relapse, conducted and sponsored by Children's Oncology Group (COG). The primary objectives of this study were to determine a recommended phase 2 dose (RP2D) and the toxicities associated with CPX-351 in pediatric and young adult patients with relapsed/refractory AML and to estimate the response rate (complete remission [CR] + complete remission with partial platelet recovery [CRp]) after CPX-351 (Cycle 1) followed by fludarabine/cytarabine/G-CSF (FLAG; Cycle 2) in children with AML in first relapse.

This study comprised 2 phases: a Dose-finding Phase and an Efficacy Phase. The Dose-finding Phase employed a modified rolling 6 design. Patients were assigned a dose of CPX-351 at the time of enrollment. The starting dose was 135 units/m^2/dose on Days 1, 3 and 5. If 135 units/m^2/dose was not tolerated, a single dose de-escalation to 100 units/m^2/dose was allowed. After completion of the Dose-finding Phase, the Efficacy Phase employed a single arm 2-stage design with patients enrolled at the RP2D determined in the Dose-finding Phase. The number of patients enrolled was dependent on the number of responses. In both phases of the trial, CPX-351 was administered intravenously (IV) over 90 minutes on Days 1, 3, and 5 in Cycle 1 and FLAG was administered in Cycle 2.

Pharmacokinetic sampling during the first cycle of treatment was required for patients enrolled in the Dose-finding Phase, and optional for patients enrolled in the Efficacy Phase of this study.

Optional studies of biomarkers of cardiac injury, novel biochemical and imaging markers of cardiotoxicity, and rare coding variants as risk factors for anthracycline-induced cardiomyopathy were also included in the study design.

Throughout the study, patients were monitored for safety and adverse events (AEs); documentation began from day 1 of study treatment and continued through the 30-day follow-up period after treatment was discontinued.

Results

A total of 38 patients provided informed consent and were enrolled in this study. All patients received a dose of 135 units/m2 CPX-351 and were included in the Safety Analysis Set.

A total of 6 patients were included in the Dose-finding Phase; of these, 4 patients (66.7%) completed planned therapy and entered the follow-up period. One subject (16.7%) experienced treatment failure, and 1 subject (16.7%) did not complete the planned therapy because the physician determined it was in the subject's best interest.

Thirty-two patients were included in the Efficacy Phase; of these, 21 patients (65.6%) completed planned therapy and entered the follow-up period. Two patients (6.3%) experienced treatment failure, and 9 patients (28.1%) did not complete the planned therapy because the physician determined it was in the subject's best interest. Overall, most patients (25/38 patients, 65.8%) completed the study.

In the Safety Analysis Set (N = 38), the majority of patients were white (68.4%) and there were slightly more female (52.6%) than male (47.4%) patients. Patients had a mean (SD) age of 10.6 (6.42) years, ranging from 1 to 21 years, with most patients (44.7%) between the ages of 2 and 12 years.

Maximum tolerated dose (MTD)

Dose limiting toxicities were defined as any of the following events that occurred after the first dose of CPX-351 during the first cycle of therapy. DLT assessment occurred during the Dose Finding Phase.

Non-hematologic DLT

Non-hematologic DLTs were defined as any ≥ Grade 3 non-hematologic toxicity that occurred after the first dose of CPX-351 that was possibly, probably or definitely related to CPX-351, and with the specific exclusion of:

a) Alopecia

b) Grade 3 fatigue, anorexia, nausea, vomiting, or diarrhea

c) Grade 3 or 4 aspartate aminotransferase (AST) or ALT elevation that improved to ≤ Grade 2 within 14 days

d) Grade 3 or 4 isolated electrolyte abnormalities that resolved, with or without intervention, to ≤ Grade 2 within 72 hours

e) Tumor lysis syndrome

f) Grade 3 or 4 fever, febrile neutropenia, or infection with or without hospitalization

g) Grade 3 rash

h) Grade 3 mucositis that resolves (with or without supportive care) to ≤ Grade 2 elevation within 14 days

i) Early nutritional intervention with total parenteral nutrition or enteral tube feeding for anorexia, nausea, or concern for poor nutritional status will not be considered a DLT

j) Grade 3 troponin elevations without EKG or other evidence of myocardial ischemia

k) Grade 3 or greater pain due to leukemia, mucositis, typhlitis, infection, or obvious injury.

Hematologic Dose-Limiting Toxicity

Hematologic DLTs were defined as failure to recover a peripheral ANC > 500/μL and non- transfusion dependent platelet count > 20,000/μL due to documented bone marrow aplasia/hypoplasia (i.e., not due to malignant infiltration) for ≥ 50 days from the start of the therapeutic cycle. Failure to recover peripheral counts due to disease involvement of the bone were not considered dose-limiting.

A pediatric phase 1 trial of CPX-351 at Cincinnati Children's Hospital (Study CPX-MA-1201) completed the initial dose level of 100 units/m2/dose on Days 1, 3, 5 with no DLTs. However, enrollment on AAML1421 began at 135 units/m2/dose on Days 1, 3, 5.

The rationale for studying this dose level included:

1. No DLTs observed with CPX-351 at 100 units/m2/dose on Days 1, 3, 5 in the Study CPX-MA-1201.

2. The DLTs in the adult Study 101 that were observed at 134 units/m2 were persistent cytopenia > 56 days (1 subject), congestive heart failure (1 subject), and hypertensive crisis (1 subject). One episode of congestive heart failure occurred during a period of sepsis and was transient. Hypertensive crises are very rare in the pediatric / adolescent and young adult population; therefore, this toxicity was not considered to be relevant to the eligible patients in this study. The FDA agreed to a starting dose of 134 units/m2/dose (this study rounds the dose to 135 units/m2) upon review of the phase 1 protocol for Study CPX-MA-1201.

3. CPX-351 at a dose of 135 units/m2/dose delivers a total daunorubicin dose of approximately 180 mg/m2, which is comparable to the liposomal daunorubicin delivered in studies with daunoxome (Kaspers 2013). Also, this dose is comparable to the 150 mg/m2 cumulative dose of daunorubicin administered during Induction I of COG studies AAML0531 and AAML1031, thus providing a dose that is comparable to published literature and potentially translatable to a randomized phase 3 study.

4. If 135 units/m2/dose is not tolerated, a single dose de-escalation to 100 units/m2/dose was allowed.

The Dose-finding Phase of Study AAML1421 demonstrated that CPX-351 at 135 units/m2/dose given on Days 1, 3, and 5 was identified as the RP2D. This dose was used in the Efficacy Phase.

1.6.2. Main study

Study AAML1421: A Phase 1/2 Study of CPX 351 Alone Followed by Fludarabine, Cytarabine, and G-CSF (FLAG) for Children with Relapsed Acute Myeloid Leukemia (AML).

Methods

Study participants

The eligibility criteria were selected to enrol patients representative of relapsed, pediatric (and young adults) AML population.

The key inclusion criteria were the following:

1. Age: Patients must be ≥ 1 year and ≤ 21 years of age at the time of enrollment.

2. Diagnosis: Patients must have had histologic verification of AML at original diagnosis, with one of the following:
   - Recurrent disease with ≥ 5% blasts in the bone marrow (M2/M3 bone marrow), with or without extramedullary disease.
   - Recurrent disease with an absolute blast count > 1,000 per microliter in the peripheral blood with or without extramedullary disease.

l) Disease Status for Dose-finding Phase:
   - Relapse patients: Patients must be in first relapse, and must not have received prior re-induction therapy.
   - Refractory patients: Patients must not have received more than 1 attempt at remission induction, which may consist of up to 2 different therapy courses. (COG AAML1031 de novo therapy including Induction I and Induction II is an example.)
   - Treatment-related AML: Patients must be previously untreated for secondary AML.

m) Disease Status for Phase 2 Efficacy Phase:
   - Relapse patients: Patients must be in first marrow relapse, and must not have received prior re-induction therapy. Donor lymphocyte infusion is considered a reinduction attempt.

5. Central nervous system (CNS) Disease: Patients must have the status of CNS1 or CNS2 only, and no clinical signs or neurologic symptoms suggestive of CNS leukemia, such as cranial palsy.

6. Performance status: Eastern Cooperative Oncology Group (ECOG) scores of 0, 1 or 2. Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.

7. Prior Therapy – patients must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, stem cell transplant (SCT) or radiotherapy prior to entering this study. All prior treatment-related toxicities must have resolved to ≤ Grade 2 prior to enrollment.

    - Myelosuppressive chemotherapy: Must not have received myelosuppressive chemotherapy within 3 weeks of entry onto this study (excluding hydroxyurea).
    - Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent such as steroids, retinoids.
    - Radiation therapy (RT): ≥ 2 weeks for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if ≥ 50% radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial BM radiation.
    - SCT: No evidence of active graft vs. host disease for at least 4 weeks. For allogeneic SCT patients, ≥ 3 months must have elapsed since transplant.
        - Must have received no more than 1 prior autologous or allogeneic SCT.
        - Patients must be off all systemic immunosuppressive therapy for at least 2 weeks, excluding hydrocortisone for physiologic cortisol replacement.
        - At least 14 days must have elapsed since receiving liposomal cytarabine (DepoCyte) by IT injection.
    - Growth factors:

        - Patients must not have received growth factors for 7 days prior to CPX-351.

        - Patients must not have received pegfilgrastim for 14 days prior to CPX-351.

8. Concomitant medication restrictions:

    - No other cancer chemotherapy or immunomodulating agents may be given while the subject is on study.
    - Corticosteroid therapy is not permitted unless administered to treat anaphylactic reactions, symptoms of Ara-C syndrome, rash possibly related to CPX-351, suspected adrenal insufficiency, or pain management (in short courses ≤ 3 days).
    - Filgrastim should only be used during Cycle 1 with the discretion of the treating physician; the pegylated formulation (pegfilgrastim) should not be used.
    - Dexrazoxane use is not permitted during the study.

<u>The key exclusion criteria were the following:</u>

1. Patients who have received > 450 mg/m^2 daunorubicin equivalents.

NOTE: For the purposes of determining eligibility for this study, the following cardiotoxicity multipliers were used to determine daunorubicin equivalents: Doxorubicin: 1, Mitoxantrone: 3, Idarubicin: 3 and Epirubicin: 0.5.

2. Patients who are currently receiving another investigational drug.
3. Patients receiving medications for treatment of left ventricular systolic dysfunction.
4. Patients with any of the following diagnoses:

- Acute promyelocytic leukemia
- Down syndrome
- Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome
- Wilson's disease and any other disorder of copper metabolism
- Juvenile myelomonocytic leukemia

5. Patients with documented active, uncontrolled infection at the time of study entry.
6. Patients with known active hepatitis B virus and hepatitis C virus infections.
7. Patients with prior allergy to daunorubicin and / or cytarabine.

- **Treatments**

Patients received up to 2 cycles of therapy as follows:

Cycle 1:

All patients received 2 doses of IT cytarabine based on age:

- At the time of diagnostic lumbar puncture, or on Day 0 of Cycle 1. Patients may have received IT cytarabine up to 1 week prior to Day 1, but at least 24 hours prior to the start of CPX-351 on Day 1.
- At the time of the Day 28-30 bone marrow biopsy (or up to 1 week prior to Day 1 of Cycle 2).

Age-based dosing was as follows: patients aged 1 to 1.99 years received 30 mg; patients aged 2 to 2.99 years received 50 mg; and patients aged ≥ 3 years received 70 mg.

CPX-351 was administered at a dose of 135 units/m^2 by central venous catheter over 90 minutes on Days 1, 3, and 5.

Cycle 2: (FLAG)

Patients received 5 mcg/kg Filgrastim (G-CSF) administered IV or subcutaneously on Days 1-5 one hour prior to each dose of fludarabine. Dosing was restarted on Day 15 and continued until the post-nadir ANC ≥ 500/µL.

Fludarabine was given at a dose of 30 mg/m^2 IV over 30 minutes on Days 1-5.

High dose cytarabine at a dose of 2000 mg/m^2 was administered by IV infusion over 1 to 3 hours on Days 1-5 (4 hours after the start of fludarabine).

Primary Objective

The primary objectives of this study were to:

- Determine a recommended phase 2 dose (RP2D) and the toxicities associated with CPX-351 in pediatric and young adult patients with relapsed / refractory AML.
- Estimate the response rate (CR + complete remission with partial platelet recovery [CRp]) after CPX-351 (Cycle 1) followed by FLAG (Cycle 2) in children with AML in first relapse.

Secondary Objectives

The secondary objectives of this study were to:

- Estimate the response rate (CR + CRp + complete remission with incomplete blood count recovery [CRi]) after 1 cycle of CPX-351.
- Describe the pharmacokinetics (PK) of plasma cytarabine and daunorubicin after CPX-351 administration to pediatric and young adult patients with relapsed / refractory AML.

Exploratory Objectives

Exploratory objectives of this study were to:

- Describe the response in biomarkers of cardiac injury to a single cycle of CPX-351.
- Explore the effect of CPX-351 on novel biochemical and imaging markers of cardiotoxicity, including plasma microRNAs and myocardial deformation.
- Explore the role of rare coding variants as risk factors for anthracycline-induced cardiomyopathy.

Outcomes/endpoints

Efficacy Variables

Primary efficacy endpoint

The primary efficacy endpoint was the proportion of patients with CR or CRp after CPX-351 (cycle 1) followed by FLAG (cycle 2). The summary was done by dose level (100 units/m2/dose and 135 units/m2/dose).

Response criteria employed revised AML International Working Group criteria (Cheson 2003) and included:

Overall Response (OR): OR rate is defined as the sum of the number of patients with CR plus those with CRp divided by the total number of evaluable enrolled patients.

Complete Remission (CR): Attainment of an M1 bone marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral blood counts (ANC ≥ 1000/μL and platelet count ≥ 100,000/μL). Flow cytometry may also be useful to distinguish between leukemia and a regenerating bone marrow. There is no requirement for bone marrow cellularity.

CR with Partial Recovery of Platelet Count (CRp): Attainment of an M1 bone marrow (< 5% blasts) and no evidence of circulating blasts or extramedullary disease and with recovery of ANC ≥ 1000/μL and platelet transfusion independence (defined as: no platelet transfusions x 1 week).

Complete Remission with Incomplete Blood Count Recovery (CRi): Attainment of an M1 bone marrow (< 5% blasts) and no evidence of circulating blasts or extramedullary disease and with ANC < 1000/μL or platelet count < 100,000/μL without platelet transfusion independence (defined as: no platelet transfusions x 1 week).

Partial Response (PR): M2 bone marrow (5% to 25% blasts) and at least a 50% decrease in bone marrow blast percent from baseline. Bone marrow must have adequate cellularity (eg, ≥ 10%, if a biopsy is performed) to determine response. PR status will not be included in calculation of response to the regimen. A repeat bone marrow aspiration within 14 days may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration nd is left to the discretion of the investigator.

Treatment Failure (TF): In the Efficacy Phase, if after Cycle 1 (CPX-351) a subject has a hypoplastic bone marrow for ≥ 60 days and failure to recover a peripheral ANC > 500/μL and a non-transfusion dependent

platelet count > 20,000/µL not due to malignant infiltration or severe infection (defined as ≥ Grade 3), they will be considered a treatment failure and will go off protocol therapy.

The definition of treatment failure includes:

a) An increase in the extent of bone marrow infiltration by leukemic cells (absolute increase of ≥ 20% blasts), OR

b) Development of extramedullary disease, OR

c) M2 marrow that does not qualify for PR status, OR

d) An M1 marrow with circulating blasts, OR

e) > 25% blasts in the bone marrow after Cycle 1 of therapy.

Relapse: Morphologic relapse after CR/CRp/CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. Should flow cytometric or molecular analyses suggest relapse (by the reappearance of a similar immunophenotype or mutation to the original leukemia) in the presence of < 5% blasts, or ≥ 5% blasts in a regenerating marrow, a repeat bone marrow(s) performed at least a week later is necessary to confirm relapse by morphologic methods. In such instances the date of recurrence is defined as the first date that more than 5% blasts were observed in the marrow. The reappearance or development of cytologically proven extramedullary disease also indicates relapse. Molecular and/or genetic relapse is characterized by reappearance of a cytogenetics or molecular abnormality.

Bone Marrow Classification:

M1 is < 5% blasts M2 is 5 to 25% blasts M3 is > 25% blasts

Evaluability for Response

A subject was considered evaluable for response if:

2. The subject met the eligibility criteria for the Efficacy Phase;

3. The subject received at least 1 dose of CPX-351 at the RP2D; and

4. The subject was under follow-up for a sufficient period to evaluate the disease at the end of Cycle 1 or met the definition of Treatment Failure.

Patients who demonstrated a CR or CRp were considered to have experienced a response. All other evaluable patients were considered non-responders. A subject who died as a result of toxicity during Cycle 1 after receiving all or part of protocol therapy were considered as non-responders.

Secondary Efficacy Endpoint

The secondary efficacy endpoint was the proportion of patients with CR or CRp after CPX-351 (cycle 1).

Sample size

Up to 50 evaluable patients (12 for the Dose-finding Phase, 38 for the Efficacy Phase) were planned. Allowing for 10% of patients being inevaluable, enrollment of up to 56 patients was planned.

Study AAML1421 was designed to evaluate a minimum of 6 patients and a maximum of 12 potential patients in the Dose-finding Phase of the study. During the course of the study, the Dose-finding Phase only needed

6 patients at Dose Level 1 and the RP2D was deemed to be 135 units/m^2/dose on Days 1, 3, 5. There was no need to further expand this portion of the study and the final 6 patients were not accrued.

In the Efficacy Phase of the study, a total of 38 evaluable patients were required. All 6 patients entering the Dose-finding Phase of the study met the criteria to be considered evaluable for response in the Efficacy Phase and were therefore included in the efficacy analysis. The study organizers and the COG statistician considered the Dose-finding Phase of the study to be complete. Similarly, the Efficacy Phase evaluation was also considered complete, with a total of 38 evaluable patients (6 patients form the Dose-finding Phase plus 32 additional patients from the Efficacy Phase). As a consequence, the final 6 patients were not accrued because they were not necessary for the evaluation of efficacy.

Randomisation and Blinding (masking)

This was an open-label, single-arm study.

Statistical methods

Efficacy Phase

The Efficacy Phase is a single arm two-stage design. The following optimal Simon two-stage design was 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.

All efficacy endpoints will be presented at a 0.05 level of significant without multiplicity adjustment.

Primary Efficacy Endpoint and Analysis

Definition

The primary efficacy endpoint is the proportion of patients with CR or CRp after CPX-351 (cycle 1) followed by FLAG (cycle 2). The summary will be done by Dose-Finding Phase and Efficacy Phase.

Primary Analysis

The proportion of patients with CR or CRp will be estimated using the Jung and Kim's method (Jung and Kim, 2004).

The 90% confidence intervals were calculated using the approach of Koyama and Chen (Koyama and Chen 2008).

For example, if m = 2 and s = 20, then the p-value = 0.0607 and the 90% CI is (0.3923, 0, 6923). No sensitivity analyses or subgroup analyses were planned.

Secondary Efficacy Endpoint

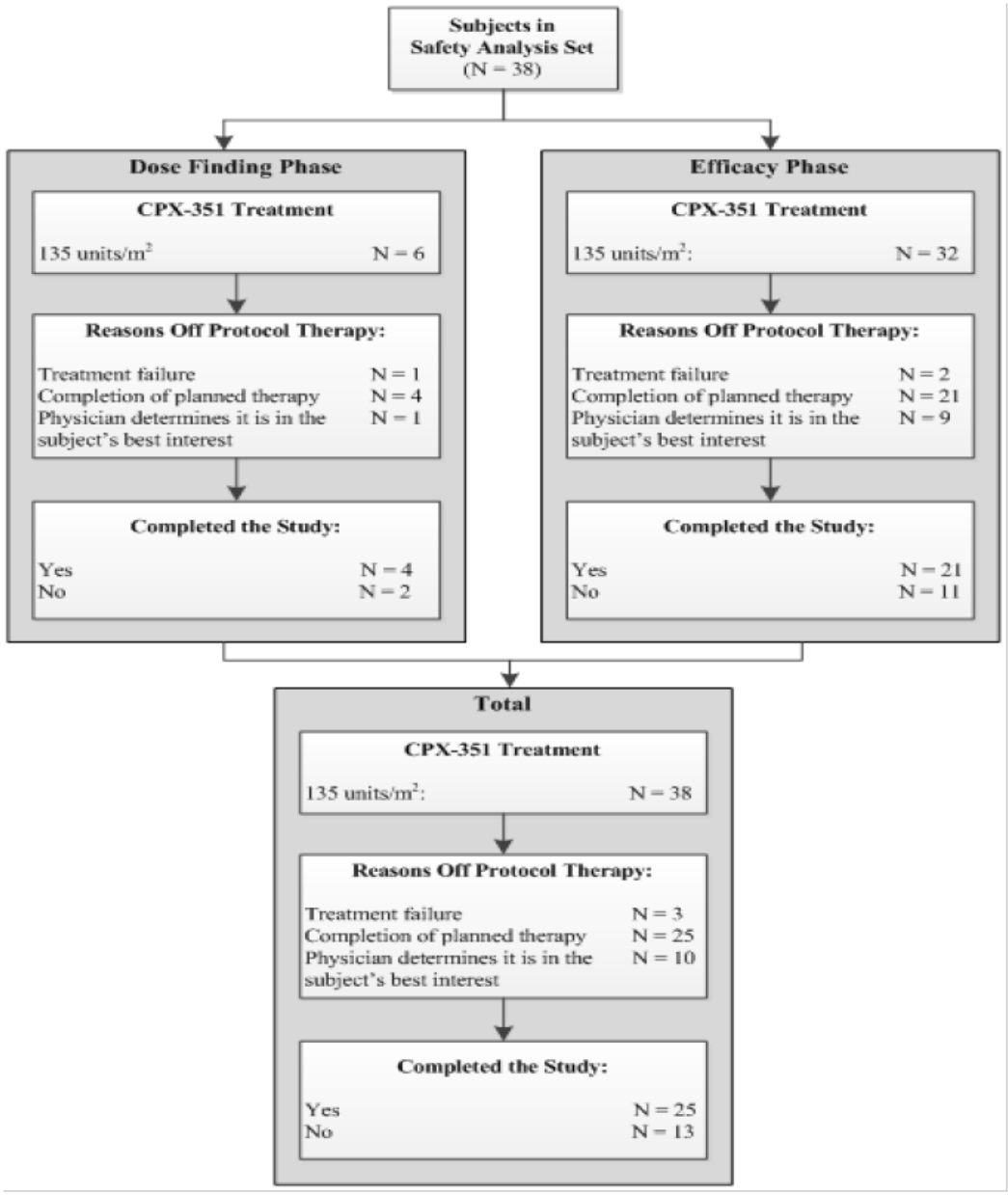
The proportion of patients with CR or CRp or CRi was estimated after 1 cycle of CPX-351 similar to the primary efficacy endpoint using Jung and Kim's method.

Results

Participant flow

The participant flow is presented in **Figure 11**.

Figure 11. Disposition of patients, Safety population



Recruitment

Between 26 April 2016 and June 2018, a total of 38 patients were randomized at 9 study centres in the USA.

Conduct of the study

The original study protocol was issued on 02 March 2016. It was subsequently amended twice: Amendment 1 was finalized on 23 February 2017, and Amendment 2 was finalized on 22 February 2018 (Version 3).

Protocol Amendment 1 (23 February 2017)

a) Results of Study 301 in adults with de novo high risk AML / MDS were added to the background.

b) The Dose-finding Phase of the study had completed as of 12 December 2016, and results were summarized and added, including:

- One DLT was experienced among the 6 patients who received 135 units/m^2 CPX-351 (and no pain related DLTs were observed).
- The RP2D was determined to be 135 units/m^2 CPX-351 and this dose was recommended for further study in the Efficacy Phase.
- Updated information in the background regarding early results from the cardiac biomarker data collected in the CPX-MA-1201 study, and added a justification to modify the serial time points collected for patients on AAML1421.
- Updated the time points for the blood samples to be drawn for the optional biomarker studies, including optional miRNA studies. (A justification for longer monitoring of miRNA was also added.)
- Added information regarding the optional PK that is included in the Efficacy Phase of the trial, including information about updated time points and the analysis of the PK samples to be drawn.
- Clarified diagnosis / disease status required for study eligibility and removed the exclusion of prior allergy to liposomal lipids.
- In eligibility criteria for the Efficacy Phase, clarified that patients must be in first marrow relapse and that donor lymphocyte infusion was considered a re-induction attempt.
- Updated schedule of required observations for the first cycle of treatment to clarify timing of CBC and differential with platelets, timing for ECHO and optional biomarker specimens (including cardiotoxicity), and timing of the optional PK blood draws.
- Added guidance to have both ejection fraction and shortening fraction calculated from the ECHO, and added a timeline for submitting CDs with ECHOs exams.

Protocol Amendment 2 (22 February 2018)

- Clarified that yearly echocardiograms should be repeated annually from the start of therapy.
- Clarified the time points for the echocardiograms and EKG.
- Updated criterion for removal from protocol therapy for the Efficacy phase from 50 to 60 days for hypoplastic marrow so that it matched the definition of Treatment Failure in Section 10.2.
- Updated the warning about concomitant use of cardiotoxic and hepatotoxic agents with CPX-351, and reformatted and updated toxicity table to match side effects outlined in the most current investigator brochure.

- Added definition of treatment failure in the Efficacy Phase of the study.
- Clarified that specimens for cytogenetic analysis were required and must have been obtained prior to initiating therapy.
- The following information regarding PK was updated: blood samples during the Efficacy phase of the study and for ordering PK kits; the Jazz contact for PKs; the blood draw volume was updated to to 2 mL since the tubes provided in the kits were 2 mL; and shipping information for PK samples.
- Added a ± of 1 hour for the Day 5, hour 6 specimen time point.
- Clarified oversight for the biomarkers of cardiotoxicity and the miRNA studies.
- Clarified time points for echocardiograms and blood biomarkers.

Baseline data

In the Safety Analysis Set (N = 38), the majority of patients were White (68.4%) and there were slightly more female (52.6%) than male (47.4%) patients (**Table 23**). Patients had a mean (SD) age of 10.6 (6.42) years, ranging from 1 to 21 years, with most patients (44.7%) between the ages of 2 and 12 years.

Most patients enrolled in the study had ECOG performance score of 0 (78.9%), and CNS status of 1 (86.8%). At enrollment, patients had AML WHO Disease Classifications in a number of categories, but the the category 'AML, other or unclassifiable' included the highest proportion of patients (36.8%). Mean (SD) cumulative prior anthracycline exposure was 344.51 (96.461) mg/m^2, which is as expected given the heavily pretreated relapsed AML population. Baseline bone marrow and hematology results were consistent with what would be expected for patients with AML. Two patients (5.3%) presented with non-CNS extramedullary disease (**Table 24**).

Table 23. 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.

Table 24. Baseline Disease Characteristics

	Number of Subjects, n (%)		
	Dose Finding Phase N = 6	**Efficacy Phase N = 32**	**Total N = 38**
Weight (kg)[a]			
n	6	32	38
Mean (SD)	62.17 (43.195)	47.63 (36.884)	49.93 (37.694)
Median	53.30	33.25	41.85
Min, Max	23.6, 145.3	9.4, 169.0	9.4, 169.0
BSA (m^2)[a]			
n	6	32	38
Mean (SD)	1.602 (0.648)	1.234 (0.574)	1.292 (0.592)
Median	1.525	1.125	1.150
Min, Max	0.90, 2.75	0.45, 2.23	0.45, 2.75
ECOG Performance Status			
0	3 (50.0)	27 (84.4)	30 (78.9)
1	3 (50.0)	4 (12.5)	7 (18.4)
2	0	1 (3.1)	1 (2.6)
CNS Status			
1	4 (66.7)	29 (90.6)	33 (86.8)
2a	1 (16.7)	1 (3.1)	2 (5.3)
2b	1 (16.7)	2 (6.3)	3 (7.9)
Radiographic Evidence of Intracranial Mass Consistent with CNS Myeloid Sarcoma			
Yes	0	0	0
No	2 (33.3)	8 (25.0)	10 (26.3)
Not evaluated	4 (66.7)	24 (75.0)	28 (73.7)
AML WHO Disease Classification			
AML with t(8;21) (q22;q22); RUNX1-RUNX1T1	1 (16.7)	4 (12.5)	5 (13.2)
AML with inv(16) (p13.1q22) or t(16;16) (p13.1;q22); CBFB-MYH11	0	1 (3.1)	1 (2.6)
AML with t(9;11) (p22;q23); MLLT3-MLL	0	1 (3.1)	1 (2.6)
Provisional entity: AML with mutated NPM1	0	2 (6.3)	2 (5.3)
Provisional entity: AML with mutated CEBPA	2 (33.3)	0	2 (5.3)
AML with myelodysplasia-related changes	0	2 (6.3)	2 (5.3)
AML with maturation	0	1 (3.1)	1 (2.6)

	Number of Subjects, n (%)		
	Dose Finding Phase N = 6	Efficacy Phase N = 32	Total N = 38
Acute myelomonocytic leukemia	0	4 (12.5)	4 (10.5)
Acute monoblastic / monocytic leukemia	1 (16.7)	4 (12.5)	5 (13.2)
Erythroleukemia, erythroid / myeloid	0	1 (3.1)	1 (2.6)
AML, other or unclassifiable	2 (33.3)	12 (37.5)	14 (36.8)
Primary Morphology of the Subject's AML			
FAB M0	1 (16.7)	0	1 (2.6)
FAB M1	1 (16.7)	0	1 (2.6)
FAB M2	0	5 (15.6)	5 (13.2)
FAB M3	0	0	0
FAB M4	0	2 (6.3)	2 (5.3)
FAB M5	0	6 (18.8)	6 (15.8)
FAB M6	0	2 (6.3)	2 (5.3)
FAB M7	0	1 (3.1)	1 (2.6)
AML not further subclassified	4 (66.7)	16 (50.0)	20 (52.6)
Cumulative Prior Anthracycline Exposure (mg/m^2)			
n	6	32	38
Mean (SD)	345.00 (120.524)	344.42 (93.610)	344.51 (96.461)
Median	369.00	325.75	325.75
Min, Max	150.0, 444.0	105.0, 444.0	105.0, 444.0
Bone Marrow Blast Percentage (%)			
n	6	32	38
Mean (SD)	57.253 (28.176)	55.119 (27.198)	55.456 (26.976)
Median	58.760	60.500	60.500
Min, Max	19.00, 91.00	5.00, 98.00	5.00, 98.00
Peripheral WBC ($10^9/L$)			
n	6	32	38
Mean (SD)	4.17 (1.300)	33.98 (131.351)	29.27 (120.735)
Median	3.75	4.05	4.00
Min, Max	2.6, 6.2	1.0, 750.0	1.0, 750.0
Peripheral Blasts (%)			
n	6	31	37
Mean (SD)	42.97 (32.754)	22.43 (29.406)	25.76 (30.471)
Median	52.50	7.00	7.00
Min, Max	2.8, 88.0	0.0, 89.5	0.0, 89.5

	Number of Subjects, n (%)		
	Dose Finding Phase N = 6	Efficacy Phase N = 32	Total N = 38
Peripheral Platelet Count ($10^9/L$)			
n	6	32	38
Mean (SD)	48.0 (35.77)	89.1 (47.73)	82.6 (48.09)
Median	39.0	75.5	71.5
Min, Max	16, 117	39, 295	16, 295
Non-CNS Extramedullary Disease at Enrollment			
Yes	0	2 (6.3)	2 (5.3)
No	6 (100)	30 (93.8)	36 (94.7)

Abbreviations: AML = acute myeloid leukemia; BSA = body surface area; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; WBC = white blood cells; WHO = World Health Organization.
[a] During development of the CSR, it was noted that 1 subject in the Efficacy Phase had 2 records included in the database for weight, height and BSA.
Note: Percentages are based on N.
Note: Weight, height and BSA measurements were taken at the beginning of Cycle 1.

The MAH states that "Data on prior and concomitant medications were noted in the subject records but were not collected on the CRF. Therefore, for the purposes of this CSR, no data on prior and concomitant medications are available in the datasets".

Numbers analysed

A total of 38 patients provided informed consent and were enrolled in this study. All patients received CPX-351 and were included in the Safety Analysis Set.

The Efficacy Evaluable Analysis Set included all patients who 1) met the eligibility criteria for the Efficacy Phase;2) received at least 1 dose of CPX-351 at the RP2D; and 3) were under follow-up for a sufficient period to evaluate the disease at the end of Cycle 1 or met the definition of treatment failure (TF).

A total of 37 patients were included in the Efficacy Evaluable Analysis Set.

Outcomes and estimation

Primary efficacy endpoint: Overall Response Rate (ORR) After CPX-351 (Cycle 1) followed by FLAG (Cycle 2).

The ORR (CR + CRp) after CPX-351 (Cycle 1) followed by FLAG (Cycle 2) was 68% using Jung and Kim's method (90% CI: 53% to 78%; p-value: < 0.001, using the approach of Koyama and Chen; **Table 25**).

When examining best response (defined as CR or CRp or CRi) after CPX-351 (Cycle 1) followed by FLAG (Cycle 2), the best response rate was 81% using Jung and Kim's method (90% CI: 67% to 89%; p-value: < 0.001, using the approach of Koyama and Chen). Best response was achieved by 21/37 patients (56.8%) after Cycle 1 and by 9/37 patients (24.3%) after Cycle 2.

Table 25. Summary of Best Response for Patients with CR, CRp or CRi over 2 Cycles

	Overall N = 37 n (%)	p[a] (90%CI)[b]	p-value[b]	p[a] (80%CI)[b]
Best Response Rate (CR)	20 (54.1)	0.59 (0.40, 0.70)	0.047	0.59 (0.43, 0.66)
Best Response Rate (CRp)	5 (13.5)	--	--	--
Best Response Rate (CRi)	5 (13.5)	--	--	--
Overall Response Rate (CR + CRp)	25 (67.6)	0.68 (0.53, 0.78)	< 0.001	0.68 (0.56, 0.76)
Stage 1	10 (27.0)	--	--	--
Stage 2	15 (40.5)	--	--	--

Subjects with Best Response of CR or CRp or CRi	30 (81.1)	0.81 (0.67, 0.89)	< 0.001	0.81 (0.70, 0.87)
Timing of Best Response (CR, CRp, CRi)				
Cycle 1	21 (56.8)	--	--	--
Cycle 2	9 (24.3)	--	--	--

Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with partial recovery of platelet count; p = proportion; PR = partial response; TF = treatment failure.
[a] Estimated using the method of Jung and Kim.
[b] Calculated using the approach of Koyama and Chen.
Percentages are based on N.
Note: Subject's best response over 2 cycles during reporting period was determined by the following order of responses (CR > CRp > CRi > PR > TF).

Secondary efficacy endpoint: Response Rate After CPX-351 (Cycle 1)

As a secondary objective of Study AAML1421, the response rate (CR + CRp + CRi) after 1 cycle of CPX-351 was 76% using Jung and Kim's method (90% CI: 61% to 85%; p-value: < 0.001, using the approach of Koyama and Chen) (5.4.2.3). A total of 7/37 patients (18.9%) had a partial response (PR) and 2/37 patients (5.4%) were diagnosed with treatment failure (TF).

During Cycle 2, 13/27 patients (48.1%) achieved CR, 7/27 patients (25.9%) achieved CRp, and 2/27 patients (7.4%) achieved CRi. No patients had a PR and 5/27 patients (18.5%) were diagnosed with TF (**Table 26**).

Table 26. Summary of Best Response

Response	Cycle 1 N = 37	Cycle 2 N = 27
CR, n (%)	14 (37.8)	13 (48.1)
CRp, n (%)	2 (5.4)	7 (25.9)
CRi, n (%)	12 (32.4)	2 (7.4)
PR, n (%)	7 (18.9)	0
TF, n (%)	2 (5.4)	5 (18.5)
Relapse, n (%)	0	0
Unevaluable, n (%)	0	0
Subjects with CR or CRp or CRi, n (%)[a]	28 (75.7)	NC
Proportion of Subjects with CR or CRp or CRi After 1 Cycle of CPX-351, p[b]	0.76	NC
90% CI[c]	0.61, 0.85	NC
p-value[c]	< 0.001	NC

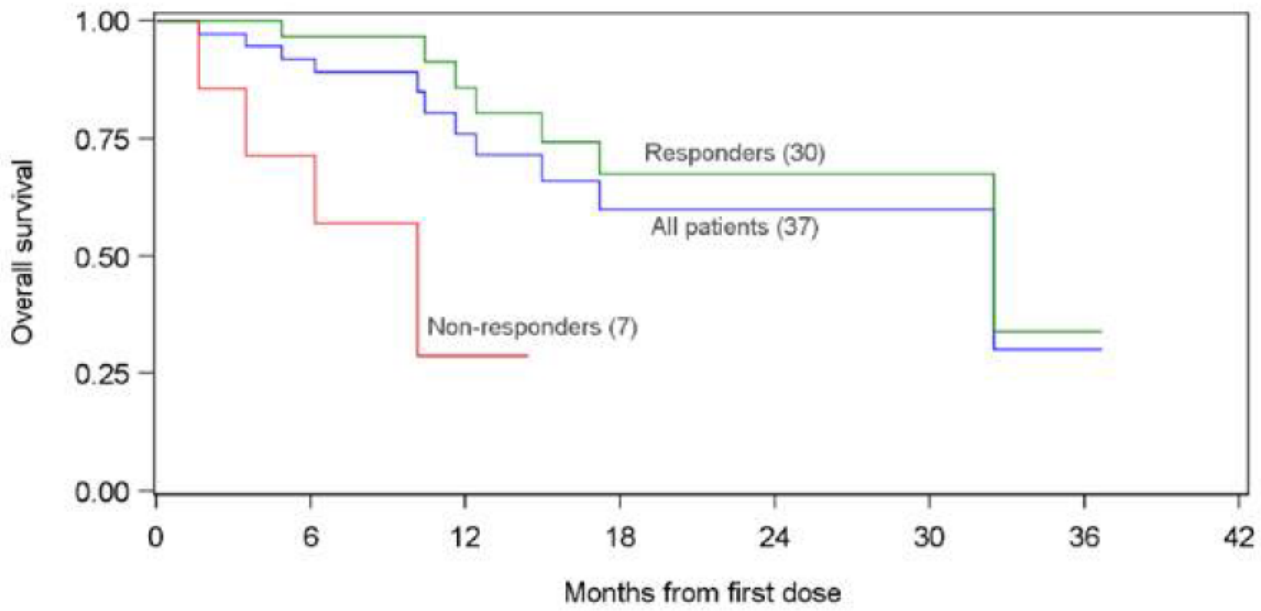
Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with partial recovery of platelet count; NC = not calculated; PR = partial response; TF = treatment failure.
[a] This includes all responses.
[b] Estimated using the method of Jung and Kim.
[c] Calculated using the approach of Koyama and Chen.
Note: Cycle 1 treatment was 135 unit/m^2 CPX-351 and Cycle 2 treatment was FLAG.
Percentages are based on N.

Of the patients classified as responders (i.e., those whose best response over 2 cycles was CR or CRp or CRi), 10/30 patients (33.3%) had cytogenetics classified as other, 6/30 patients (20.0%) had inv(16); t(8;21), and 6/30 patients (20.0%) had unknown cytogenetics.

Exploratory Analysis: Overall Survival

The median OS was estimated as 32.5 months for all 37 efficacy evaluable patients using the Kaplan-Meier method (26/37 patients [70.3%] survived at the time of analysis; **Figure 12**). The median OS was estimated as 32.5 months for the 30 responders (ie, patients with best response of CR or CRp or CRi over 2 cycles; 23/37 patients [62.2%] survived at the time of analysis). The median OS was estimated as 10.1 months for the 7 non-responders (i.e., patients who had a PR or were diagnosed with TF; 3/37 [8.1%] survived at the time of analysis).

Figure 12. Summary of Overall Survival (Efficacy Evaluable Analysis Set)



Abbreviations: CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with partial recovery of platelet count.
Note: Responders are defined as patients whose best response was CR or CRp or CRi and non-responders if otherwise.

Ancillary analyses

No formal subgroup analyses were planned or conducted.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27. Summary of Efficacy for AAML1421

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

Study identifier	AAML1421 (NCT02642965)		
Design	Single-arm, open-label, multi-institutional		
	Duration of main phase:		29 April 2016 (first subject screened) 30 June 2019 (primary database cut-off)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase		Not applicable
Hypothesis	The null hypothesis that the overall response rate with the study treatment is ≤ 40% versus the alternative hypothesis that the response rate with the study treatment is ≥ 60%.		
Treatments groups	Single arm		Cycle 1: CPX-351 was administered at a dose of 135 units/m^{2*} by central venous catheter over 90 minutes on Days 1, 3, and 5. **1 unit of Vyxeos contains 0.44 mg daunorubicin and 1 mg cytarabine.*
			Cycle 2: Subjects received 5 µg/kg Filgrastim (G-CSF) administered IV or subcutaneously on Days 1-5 one hour prior to each dose of fludarabine. Dosing was restarted on Day 15 and continued until the post-nadir ANC ≥ 500/µL. Fludarabine was given at a dose of 30 mg/m^2 IV over 30 minutes on Days 1-5. High dose cytarabine at a dose of 2000 mg/m^2 was administered by IV infusion over 1 to 3 hours on Days 1-5 (4 hours after the start of fludarabine).
Endpoints and definitions	Primary endpoint	Safety	The recommended phase 2 dose (RP2D) determined by toxicities associated with CPX-351 in pediatric and young adult participants with relapsed / refractory AML.
		Efficacy	The response rate (CR + complete remission with partial platelet recovery [CRp]) after CPX-351 (Cycle 1) followed by FLAG (Cycle 2) in children with AML in first relapse.
	Secondary endpoint	Pharmacokinetics (PK)	The PK of plasma cytarabine and daunorubicin after CPX-351 administration to pediatric and young adult participants with relapsed / refractory AML.
		Efficacy	The response rate (CR + CRp + complete remission with incomplete blood count recovery [CRi]) after 1 cycle of CPX-351.
Database lock	30 June 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Safety Analysis Set (N=38) for the RP2D and Efficacy Evaluable Set (N=37) for all efficacy endpoints.		
Descriptive statistics and estimate variability	Treatment group		CPX-351
	Number of participants		37

Efficacy	CR + CRp (overall response rate) after up to 2 cycles (%)	68
	CR or CRp or CRi (best response rate) after up to 2 cycles (%)	81
	CR + CRp + CRi after cycle 1 (CPX-351) (%)	76
	CR or CR or CRi (best response) after receiving Cycle 1 (CPX-351) (%)	56.8
	CR or CR or CRi (best response) after receiving Cycle 2 (FLAG) (%)	24.3
	Median OS estimate (months)	32.5
Descriptive statistics and estimate variability Safety	Treatment-related deaths during the study	None
	Dose limiting toxicity (DLT) (n/N)	1/6
	Serious TEAE (%)	55.3
	Most commonly reported serious TEAE (%)	Febrile neutropenia (28.9)
	TEAE any grade (%)	89.5
	Most commonly reported TEAE any grade (%)	Febrile neutropenia (47.4) Rash maculo-papular (47.4) QT prolongation (28.9)
	Mean and median left ventricular shortening fraction (LVSF) and left ventricular ejection fraction (LVEF)LVSF and LVEF	Remained near or within normal limits
Notes		

Supportive study

The details of this study have been presented previously both in the PK section and Dose response studies section in this report.

Study Design

Study CPX-MA-1201 was a phase 1, single-center pilot study to assess the PK, toxicity and tolerability of CPX-351 in pediatric and young adult patients with relapsed / refractory hematologic malignancies.

The secondary efficacy objective of this study was to estimate the overall response rate (ORR) to a single course of CPX-351 to young patients with recurrent or refractory hematologic malignancies.

Study population

A total of 27 patients were enrolled in the study, received at least 1 dose of study drug, and comprised the safety population. A total of 9 patients were included in the Dose Exploration Phase. Of these, 5 patients received a dose of 134 units/m2 CPX-351 and 4 patients received a dose of 100 units/m^2 CPX-351. All 9 patients (100.0%) completed course 1 of therapy and entered the follow-up period.

Among patients who received 134 units/m^2 CPX-351, 4/5 (80.0%) patients completed the 6-month follow-up period, and 1/5 (20.0%) subject died during follow-up. Among patients who received 100 units/m^2 CPX-351, 2/4 (50.0%) patients completed the 6-month follow-up period, and 2/4 (50.0%) patients died during follow-up.

A total of 18 patients were included in the Expanded Phase, and all received a dose of 100 units/m^2 CPX-351. A total of 17/18 patients (94.4%) completed course 1 therapy and entered the follow-up period. One subject went off protocol therapy because of disease progression and pursuit of other therapy. A total of 11/18 (61.1%) patients completed the 6-month follow-up period, and 7/18 (38.9%) patients died during follow-up.

The majority of patients were white (77.8%) and there were slightly more female (51.9%) than male (48.1%) patients. Patients had a mean (SD) age of 6.7 (5.90) years, ranging from 1 to 19 years, with most patients (59.3%) in the age group 2 to < 12 years. No patients aged < 1 year were enrolled. The majority of patients enrolled had AML (23/27 patients, 85.2%) and 4/27 patients (14.8%) had ALL.

Efficacy

A secondary objective of Study CPX-MA-1201 was to estimate the ORR to a single course of CPX-351.

Among patients with AML who received 100 units/m^2 CPX-351, 3/18 patients (16.7%) achieved CR and 3/18 patients (16.7%) achieved CRi for an ORR of 33.3% (6/18 patients; table 5.4.2.6).

Among patients with AML who received 134 units/m^2 CPX-351, 2/5 patients (40.0%) achieved CR and no patients achieved CRi for an ORR of 40.0% (2/5 patients; Table 5.4.2.6).

No patients with ALL responded to treatment (**Table 28**).

Table 28. Summary of Response for Patients with AML (Safety Analysis Set)

	Number of Subjects, n (%)			
	Dose Exploration Phase		Expanded Phase	Overall
	100 units/m^2 N = 1	134 units/m^2 N = 5	100 units/m^2 N = 17	100 units/m^2 N = 18
AML (N = 23)				
CR	0	2 (40.0)	3 (17.6)	3 (16.7)
CRp	0	0	0	0
CRi	0	0	3 (17.6)	3 (16.7)
Overall Response Rate[a] (CR + CRp + CRi)	0	2 (40.0)	6 (35.3)	6 (33.3)
PR	0	0	0	0
TF	0	3 (60.0)	10 (58.8)	10 (55.6)
Unevaluable	1 (100)	0	1 (5.9)	2 (11.1)

Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with partial recovery of platelet count; PR = partial response; TF = treatment failure.
[a] The overall response rate shown includes the 2 subjects who were unevaluable.
Note: Percentages are based on N.

1.6.3. Discussion on clinical efficacy

With this application, the MAH was initially seeking approval for the following indication for Vyxeos

liposomal: "*Vyxeos liposomal is indicated for the treatment of relapsed or refractory AML in paediatric and young adult patients aged 1 to 21 years old.*". After receiving the questions from the CHMP, the MAH decided to not pursue the request for the paediatric indication in Relapse or Refractory Acute Myeloid Leukaemia (R/R AML). Therefore, the MAH is only proposing updated text within Sections 4.4, 4.8, 5.1 and 5.2 of the SmPC. Consequently, the MAH provided responses only to questions related to data proposed to be included in the SmPC.

Clarifications in relation to proposed indication were considered necessary. The data provided could be possibly acceptable for the relapsed, paediatric population. However, there are data currently from only 8 relapsed, young adults. The proposed upper age limit of 21 years was not clinically justified, but rather driven by age range of the available data. In addition to that, no specific efficacy and safety results according to different age groups were provided and suitability of the proposed dosing for young adults was questioned. Therefore, the proposed indication (including also young adult relapsed patients) was to be further justified or the wording of the indication to be modified accordingly.

Moreover, the MAH was asked to justify the inclusion of refractory patients into proposed indication because the information with regard to exact number of patients with either relapsed AML or with refractory AML was missing. Specifically, as cytarabine and anthracycline combination therapies are already standard part of first line therapy, the MAH was asked to discuss whether patients, who were refractory to first line therapy, may still respond to second line cytarabine-daunorubicine therapy. In its response, the MAH has clarified that all patients were with relapsed AML. However, the MAH has not provided requested efficacy and safety data per age cohort nor provided justification regarding the acceptability of the proposed posology for young adults or refractory paediatric patients. Since the MAH no longer pursuing the indication for paediatric patients with R/R AML these issues are not pursued further.

Acute myeloid leukaemia (AML) is a biologically heterogeneous disease that can be classified into 3 distinct categories based on clinical ontogeny: de novoAML which arises in the absence of an identified exposure or prodromal stem cell disorder (like in MDS). Secondary AML (s-AML) represents transformation of an antecedent diagnosis of myelodysplastic syndrome (AML-MRC) or myeloproliferative neoplasm (MPN), therapy-related AML (tAML) develops as a late complication in patients with prior exposure to leukaemogenic therapies.

Long-term survival rates of paediatric AML patients are currently 70% or even higher. Compared to adults, children with AML have superior outcomes due to fewer adverse genetic mutations and the ability to tolerate the high-intensity chemotherapy currently necessary for cure. Regarding novel agents and treatment modalities, drugs such as venetoclax, monoclonal antibodies, and cellular therapies are investigated also in paediatric AML.

Relapse after initial AML therapy is associated with poor prognosis and the only consistently curative therapy for relapsed AML is a HSCT.

The MAH has provided data from pivotal phase II study (AAML1421) and supportive phase I study (CPX-MA-1201). The dose of CPX-351 used in study AAML1421 was 135 units/m^2 versus 100 unit/m^2 in study CPX-MA-1201, respectively. Due to that, direct comparison of efficacy results (after 1 cycle of CPX-351) between these two studies is not possible.

Study AAML1421 (phase II) enrolled patients paediatric and young adult patients with relapsed AML. Study CPX-MA-1201 (phase I) on the other hand enrolled paediatric and young adult patients with relapsed / refractory hematologic malignancies (AML and ALL).

Design and conduct of clinical studies

Study AAML1421

The efficacy of CPX-351 in paediatric and young adult patients with relapsed AML (up to 21 years old) is based mainly on one, open-label, single-arm study AAML1421. It was conducted and sponsored by the Children's Oncology Group (COG) and the MAH was not involved in the study conduct but received the data from the Sponsors and summarized the results of the study for the purposes of regulatory submission. The study is considered of adequate design with appropriate clinical endpoints for the target indication of relapsed, paediatric AML [(with the primary efficacy endpoint of the proportion of patients with CR or CRp after CPX-351 (cycle 1) followed by FLAG (cycle 2)].

This study comprised 2 phases: a dose-finding phase and an efficacy phase. During the dose-finding phase, a modified rolling 6 design was employed. Subjects were assigned a dose of CPX-351 at the time of enrollment. The starting dose was 135 units/m^2/dose (i.e. 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine) on Days 1, 3 and 5. If the starting dose was not tolerated, a single dose de-escalation to 100 units/m^2/dose was allowed.

Targeting HSCT should have been given considerably more value. The only long-term curative treatment option in relapsed AML patients is HSCT (HSCT is recommended as post-remission (CR2) management in all suitable relapsed AML patients). Due to that, all possible patients eligible for this procedure should be offered and targeted to proceed to this treatment. The MAH has clarified that prior HSCT was recorded in 10 out of 38 patients (26.3%).

The MAH has used a method from Jung and Kim to calculate the number of responders (both with regard to primary and secondary efficacy endpoints). However, the response rate has now been presented as a simple proportion of responders and the corresponding Clopper-Pearson confidence interval in the SmPC as requested.

The study inclusion/exclusion criteria reflect the target population of relapsed AML patients. 10 out 38 patients did not complete the study because the physician determined it was in the subject's best interest not to continue in the study. The MAH has clarified that seven patients with CR, CRi, or CRp after cycle 1 had HCT after discontinuing study treatment. One patient had treatment failure and for the remaining two patients there is no further information. The MAH`s response is considered adequate. The MAH`s reasoning that the treatment approach to relapsed/ refractory pediatric AML between US and European investigators is essentially the same, is also acceptable.

Additional data from one phase 1 study has been presented to further support the efficacy of CPX-351: Study CPX-MA-1201. In this phase I (PK, MTD) single arm study, a total of 23 relapsed, pediatric AML patients were treated with single course of CPX-351.

Efficacy data and additional analyses

A total of 38 subjects were enrolled in this study:

- Six subjects were included in the dose-finding phase, all of whom received a CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine (i.e. 135 units/m^2/dose). Of the 6 subjects in the dose-finding phase, 1 subject experienced a DLT (a serious adverse event of Ejection fraction decreased) at the dose level of 135 units/m^2/dose. The remaining subjects did not experience DLTs, and 135 units/m^2/dose (i.e. 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine) was the RP2D.
- Thirty-two subjects were included in the Efficacy Phase, and all received CPX-351 135 units/m^2/dose.

In the pivotal study AAML1421, the primary efficacy endpoint (after CPX-351 (Cycle 1) followed by FLAG (Cycle 2)) displayed an ORR (CR + CRp) of 68% and the best response rate (CR + CRp + CRi) of 81%. However, the MAH has used an unconventional method to calculate the number of responders and should

provide the response rate as a simple proportion of responders and the corresponding Clopper-Pearson confidence interval.

In addition, to justify the potential benefit of the treatment, the MAH was asked to provide data with regard to the use of HSCT as consolidation in patients achieving response. The MAH has not provided the requested data. However, since the MAH no longer pursuing the indication for pediatric patients with R/R AML, this issue is not actual any more.

The secondary efficacy endpoint (after 1 cycle of CPX-351) displayed a response rate (CR + CRp) of 43.2 % and the best response rate (CR + CRp + CRi) of 76%. The same concern applies also here with regard to actual response rates: the MAH was requested to provide the response rate as a simple proportion of responders and the corresponding Clopper-Pearson confidence interval. Thus, while treatment with CPX-351 seem to achieve substantial results on its own, the second treatment course with FLAG increases the efficacy even further. However, there are similar concerns with regard to missing information and contextualisation of the results as mentioned with the interpretation of results of the primary efficacy endpoint.

The median OS was estimated as 32.5 months for all 37 efficacy evaluable subjects. The result of this post-hoc exploratory analysis should be further contextualised by the MAH. Updated follow-up data and especially outcome data of patients treated with allo-HSCT as consolidation to establish the clinical benefit of the proposed treatment with Vyxeos liposomal should be provided. The MAH has not provided the requested long-term efficacy data which is acceptable since the MAH is no longer pursuing the indication for paediatric patients with R/R AML.

Study CPX-MA-1201

With the 100 unit/m^2 dose the ORR was 33.3% and 16.7% of the patients achieved CR. The MAH has only briefly contextualised these results by stating that "the observed ORR values were consistent with children and young adults with relapsed/refractory AML who were predominantly heavily pre-treated (Gorman 2010; Quarello 2015; Cooper 2017; Jaiswal 2016)".

Due to limited number of patients in this study, the efficacy results of this small SAT could be regarded descriptive at best.

1.6.4. Conclusions on the clinical efficacy

In the pivotal clinical study AAML1421, treatment with CPX-351 resulted in an ORR (CR + CRp) of 68% and the best response rate (CR + CRp + CRi) of 81% in relapsed paediatric patients. The reported CR rate of 54%, supported by the CR/CRp/CRi rate, is considered promising for the high-risk AML study population.

The indication for the treatment of relapsed or refractory AML in paediatric and young adult patients aged 1 to 21 years old is no longer pursued, and only updating the text within Section 4.4, 5.1 and 5.2 of the SmPC is proposed. The response rate is presented as a simple proportion of responders and the corresponding Clopper-Pearson confidence interval.

Since the MAH no longer pursuing the indication for paediatric patients with R/R AML all outstanding issues that were raised during the evaluation of the clinical efficacy are not further pursued.

1.7. Clinical safety

Introduction

To support this variation, the MAH has submitted safety data from the following 2 studies in *paediatric/ young adult* subjects with AML (and ALL) and Study AAML1421 and Study CPX-MA-1201, described in Section 1.6 of this report.

For the key baseline demographic patient and disease characteristics and the patient flow for the pivotal study AAML1421, see efficacy section **Table 23** and **Figure 11**., respectively.

Pooling of paediatric safety data from the two studies was not performed, because of differences in the characteristics of the two available studies.

Patient exposure

Study AAML1421

In Study AAML1421 all 38 subjects (100%) received 1 cycle of therapy with CPX-351 followed by FLAG (Cycle 2). All but 1 subject (37/38 subjects, 97.4%) received 3 CPX-351 doses of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine; 1 subject received 2 CPX-351 doses of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine. Overall, the mean (SD) cumulative doses of daunorubicin and cytarabine received were 220.1 (106.50) mg and 500.1 (242.04) mg, respectively.

Recommended phase 2 dose: During the Dose-finding Phase, CPX-351 dosing was initiated at 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine administered once daily to subjects on Days 1, 3, and 5. A total of 1/6 subjects experienced a DLT (ejection fraction decreased) and this dose was determined to be the RP2D.

Study CPX-MA-1201

A total of 22 subjects received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (4 in the Dose Exploration Phase and 18 in the Expansion Phase), and 5 subjects (all in the Dose Exploration Phase) received a CPX-351 dose of 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine. All 27 subjects (100%) received 1 course of therapy. Overall, the mean (SD) cumulative dose of daunorubicin and cytarabine received were 135.7 (80.41) mg and 308.5 (182.75) mg, respectively.

Maximum tolerated dose: During the Dose Exploration Phase, CPX-351 dosing was initiated at 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine in 9 subjects. No DLTs were observed and dosing was escalated to 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine. At this dose, 2/5 subjects experienced DLTs (1 DLT of Grade 3 headache and 1 DLT of Grade 3 pain). Therefore, the MTD was declared to be a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m2 cytarabine administered IV once daily on Days 1, 3 and 5. This dose was used in the Expanded Phase. One subject in the Expanded Phase experienced a DLT PT Platelet count decreased (Grade 4) which resolved in 2 days. The investigator considered the event to be probably related to CPX-351.

Premedications and Concomitant Medications

Paediatrics and Young Adults

Subjects were not routinely premedicated for hypersensitivity or for potential infusion-related reactions prior to the first infusion of the first treatment course. If a subject developed a hypersensitivity reaction, then the subject should have been premedicated at subsequent infusions. Subjects were also allowed to

receive ongoing supportive and palliative care (e.g., pain control) as clinically indicated throughout each study.

As expected, the RR-AML subject populations were heavily pre-treated. For AAML1421, the baseline mean prior anthracycline use is reported as 344.51 (96.461) mg/m^2. For Study CPX-MA-1201, based on protocol inclusion criteria, all subjects reported receiving prior therapy to treat their AML or ALL. Specifically, all subjects reported receiving chemotherapy; 10/23 subjects with AML (43.5%) and 1/4 subject with ALL (25.0%) reported receiving a transplant; and 1/23 subjects with AML (4.3%) and 3/4 subjects with ALL (75.0%) reported receiving radiation.

Considering the study population of subjects with RR-AML undergoing aggressive chemotherapy concomitant medications used across the paediatric Studies AAML1421 and CPX-MA-1201 were as expected in this context. For these studies the subjects were allowed to receive ongoing supportive care as clinically indicated throughout the study, however, no data on concomitant medications are available in the datasets.

Adverse events

A summary of AEs that occurred on or after the first dose of study medication administration is provided below for the pediatric RR-AML studies (AAML1421 and CPX-MA-1201).

Treatment-emergent adverse events that occurred after study medication administration (regardless of relatedness to study medication) were reported for each dose level.

Study AAML1421

The majority of subjects experienced TEAEs and related TEAEs during the study. More than half of subjects experienced serious TEAEs, and related serious TEAEs. The majority of subjects (89.5%) experienced events categorized as ≥ Grade 3, with 4 subjects (10.5%) experiencing Grade 4 TEAEs, and 1 subject (2.6%) experiencing a Grade 5 TEAE. No subjects went off protocol therapy due to unacceptable toxicity.

Table 29. Study AAML1421 Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Number of Subjects, n (%)		
	Dose-finding Phase N = 6	**Efficacy Phase N = 32**	**Overall N = 38**
Subjects with any TEAE	**6 (100)**	**28 (87.5)**	**34 (89.5)**
Subjects with any Serious TEAE	6 (100)	15 (46.9)	21 (55.3)
Subjects with any Related TEAE	5 (83.3)	25 (78.1)	30 (78.9)
Subjects with any Serious Related TEAE	5 (83.3)	15 (46.9)	20 (52.6)
Subjects with any TEAE by Maximum Grade	**6 (100)**	**28 (87.5)**	**34 (89.5)**
Grade 1	0	0	0
Grade 2	0	0	0
Grade 3	4 (66.7)	25 (78.1)	29 (76.3)
Grade 4	1 (16.7)	3 (9.4)	4 (10.5)
Grade 5	1 (16.7)	0	1 (2.6)
Grade 3 to 5	6 (100)	28 (87.5)	34 (89.5)

Abbreviations: AE = adverse event; CRF = case report form; TEAE = treatment-emergent adverse event. Note: A TEAE was defined as any event with an onset date on or after the treatment start date in the eligibility CRF up to 30 days after the last reporting period end date, or any ongoing event that worsened in severity after the date of the first dose of study drug up to and including 30 days after the last reporting period end date.
Note: Adverse event severities were graded by the investigator as Grade 1: mild, 2: moderate, 3: severe or medically significant but not immediately life-threatening, 4: life-threatening, or 5: death. Severity was captured in the CRF question "AE Grade".

Note: Relationship to study drug was identified using a scale of definite, probable, possible, unlikely, and unrelated and was assessed by the investigator and captured in the CRF question "AE attribution to CPX-351." A related TEAE was a response of "possible, probable, and definite" to the CRF question "AE attribution to CPX-351".
Note: Percentages are based on N. Note: Subjects received Cycle 1 CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine treatment in Dose-finding Phase and Efficacy Phase.

Study CPX-MA-1201

All subjects experienced TEAEs during the study (Table 30). In the Dose Exploration Phase, all subjects who received Dose Level 1 (CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine) experienced TEAEs and related TEAEs. A total of 2/4 subjects (50.0%) experienced SAEs and 2/4 subjects (50.0%) experienced related SAEs. No subjects experienced DLTs. Dosing was subsequently escalated to test Dose Level 2 (CPX-351 dose of 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine). At this Dose Level all 5 subjects experienced TEAEs, SAEs, or related TEAEs or related SAEs. Two subjects (40.0%) experienced events classified as DLTs. Therefore, all subjects in the Expanded Phase received Dose Level 1 (CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine).

In the Expanded Phase, all 18 subjects experienced TEAEs and related TEAEs. A total of 16 subjects (88.9%) experienced SAEs and 15 subjects (83.3%) experienced related SAEs. One subject in the Expanded Phase experienced an event classified as a DLT.

Among the 22 subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (regardless of whether it was in the Dose Exploration Phase or the Expanded Phase), all experienced TEAEs and related TEAEs. A total of 18/22 subjects (81.8%) experienced SAEs, and 17 subjects (77.3%) experienced related SAEs.

All subjects experienced Grade 3 and Grade 4 events. No subjects experienced Grade 5 TEAEs.

The AEs/SAEs at a higher dose of CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine (Study AAML1421) were similar to those at a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (Study CPX-MA-1201) in the pediatric population and young adults up to 21 years of age.

Table 30. Study CPX-MA-1201 Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Number of Subjects, n (%)			
	Dose Exploration Phase		**Expanded Phase**	**Overall**
	100 units/m^2 N = 4	**134 units/m^2 N = 5**	**100 units/m^2 N = 18**	**100 units/m^2 N = 22**
Subjects with any TEAE[i)]	**4 (100)**	**5 (100)**	**18 (100)**	**22 (100)**
Subjects with any Serious TEAE[Error! Reference source not found.]	2 (50.0)	5 (100)	16 (88.9)	18 (81.8)
Subjects with any Related TEAE[ii)]	4 (100)	5 (100)	18 (100)	22 (100)
Subjects with any Serious Related TEAE[Error! Reference source not found.]	2 (50.0)	5 (100)	15 (83.3)	17 (77.3)
Subjects with any DLT	0	2 (40.0)	1 (5.6)	1 (4.5)
Subjects with any TEAE[Error! Reference source not found.] by Severity				
Grade 1	0	5 (100)	4 (22.2)	4 (18.2)
Grade 2	1 (25.0)	4 (80.0)	12 (66.7)	13 (59.1)
Grade 3	4 (100)	5 (100)	18 (100)	22 (100)
Grade 4	4 (100)	5 (100)	18 (100)	22 (100)

	Number of Subjects, n (%)			
	Dose Exploration Phase		Expanded Phase	Overall
	100 units/m² N = 4	134 units/m² N = 5	100 units/m² N = 18	100 units/m² N = 22
Grade 5	0	0	0	0
Grade 3 to 5	4 (100)	5 (100)	18 (100)	22 (100)

Abbreviations: AE = adverse event, CRF = case report form; DLT = dose limiting toxicity; TEAE = treatment-emergent adverse event. **Error! Reference source not found.**A TEAE was defined as any event with onset date on or after the first dose of study drug until 30 days after the last dose, or any ongoing event that worsened in severity after the date of the first dose of study drug up to and including 30 days after the last dose of study drug. [ii]) A TEAE was classified as related based on a response of "Possible", "Definite", "Probably" to the CRF question "AE attribution to CPX-351". Note: Percentages were based on N.
Note: 1 unit CPX-351 = 1 mg cytarabine and 0.44 mg daunorubicin. Note: Treatment-emergent adverse event severity was graded by the investigator as Grade 1: mild, 2: moderate, 3: severe or medically significant but not immediately life-threatening, 4: life-threatening, or 5: death. Maximum grade was captured in the CRF.

Common Adverse Events

Study AAML1421

Overall (N = 38 subjects), the reported TEAEs were most frequently categorized in the SOCs Infections and Infestations (20 subjects, 52.6%), Blood and Lymphatic System Disorders (19 subjects, 50.0%), Investigations (18 subjects, 47.4%), and Skin and subcutaneous (SC) Tissue Disorders (18 subjects, 47.4%) (**Table 31**.). The most frequently reported TEAEs (i.e., those occurring in ≥ 25% of subjects) listed by decreasing frequency were Febrile neutropenia, Rash maculopapular, and Electrocardiogram QT prolonged.

The high incidences of TEAEs related to myelosuppression were expected given the known consequences of intensive chemotherapy and are consistent with the known safety profile for this agent. Of note, subjects were on concomitant therapy with other drugs known to prolong the QT interval (e.g., azole antifungal prophylaxis).

Table 31. Study AAML1421 Treatment-emergent Adverse Events Reported in ≥ 5% of Subjects, by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Dose-finding Phase N = 6	Efficacy Phase N = 32	Overall N = 38
Subjects with any TEAE	**6 (100)**	**28 (87.5)**	**34 (89.5)**
Infections and Infestations	**4 (66.7)**	**16 (50.0)**	**20 (52.6)**
Skin infection	1 (16.7)	3 (9.4)	4 (10.5)
Sepsis	1 (16.7)	2 (6.3)	3 (7.9)
Device related infection	0	2 (6.3)	2 (5.3)
Lung infection	0	2 (6.3)	2 (5.3)
Mucosal infection	0	2 (6.3)	2 (5.3)
Upper respiratory tract infection	0	2 (6.3)	2 (5.3)
Anorectal infection	1 (16.7)	0	1 (2.6)
Escherichia infection	1 (16.7)	0	1 (2.6)
Septic shock	1 (16.7)	0	1 (2.6)
Staphylococcal infection	1 (16.7)	0	1 (2.6)

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Dose-finding Phase N = 6	Efficacy Phase N = 32	Overall N = 38
Blood and Lymphatic System Disorders	**3 (50.0)**	**16 (50.0)**	**19 (50.0)**
Febrile neutropenia	3 (50.0)	15 (46.9)	18 (47.4)
Investigations	**2 (33.3)**	**16 (50.0)**	**18 (47.4)**
Electrocardiogram QT prolonged	2 (33.3)	9 (28.1)	11 (28.9)
Alanine aminotransferase increased	0	3 (9.4)	3 (7.9)
Aspartate aminotransferase increased	0	2 (6.3)	2 (5.3)
Ejection fraction decreased	1 (16.7)	1 (3.1)	2 (5.3)
Gamma-glutamyltransferase increased	0	2 (6.3)	2 (5.3)
Streptococcus test positive	1 (16.7)	0	1 (2.6)
Skin and Subcutaneous Tissue Disorders	**1 (16.7)**	**17 (53.1)**	**18 (47.4)**
Rash maculopapular	1 (16.7)	17 (53.1)	18 (47.4)
Metabolism and Nutrition Disorders	**2 (33.3)**	**7 (21.9)**	**9 (23.7)**
Hypokalaemia	2 (33.3)	3 (9.4)	5 (13.2)
Hyperglycemia	0	3 (9.4)	3 (7.9)
Decreased appetite	0	2 (6.3)	2 (5.3)
Gastrointestinal Disorders	**1 (16.7)**	**4 (12.5)**	**5 (13.2)**
Colitis	0	2 (6.3)	2 (5.3)
Dysphagia	1 (16.7)	0	1 (2.6)
Respiratory, Thoracic and Mediastinal Disorders	**1 (16.7)**	**4 (12.5)**	**5 (13.2)**
Epistaxis	0	2 (6.3)	2 (5.3)
Hypoxia	1 (16.7)	0	1 (2.6)
General Disorders and Administration Site Conditions	**2 (33.3)**	**2 (6.3)**	**4 (10.5)**
Pyrexia	1 (16.7)	1 (3.1)	2 (5.3)
Death	1 (16.7)	0	1 (2.6)
Nervous System Disorders	**1 (16.7)**	**2 (6.3)**	**3 (7.9)**
Hemiparesis	1 (16.7)	0	1 (2.6)

Abbreviations: CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event. Note: A TEAE was defined as any event with an onset date on or after the treatment start date in the eligibility CRF up to 30 days after the last reporting period end date, or any ongoing event that worsened in severity after the date of the first dose of study drug up to and including 30 days after the last reporting period end date. Note: Multiple entries for an individual subject under each SOC / PT are only counted once. Note: Some SOCs may have achieved the 5% threshold, but if no underlying PTs achieved the 5% threshold, the SOC is not displayed. Note: Percentages of subjects are based on N. Note: Subjects received Cycle 1 CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine treatment in Dose-finding Phase and Efficacy Phase. Note: MedDRA version 21.0.

Table 32. TEAEs in ≥ 25% of Subjects at 134 units/m2, by grades 3-5, SOC and PT

System Organ Class Preferred Term	Grade 3	Grade 4	Grade 5	Any Grade
Subjects with any TEAE	**5 (100)**	**5 (100)**	**0**	**5 (100)**
Blood and Lymphatic System Disorders	**5 (100)**	**0**	**0**	**5 (100)**
Anaemia	5 (100)	0	0	5 (100)
Febrile neutropenia	5 (100)	0	0	5 (100)
Investigations	**3 (60.0)**	**5 (100)**	**0**	**5 (100)**
Platelet count decreased	1 (20.0)	4 (80.0)	0	5 (100)
Neutrophil count decreased	0	4 (80.0)	0	4 (80.0)
Lymphocyte count decreased	0	3 (60.0)	0	3 (60.0)
White blood cell count decreased	0	3 (60.0)	0	3 (60.0)
Skin and Subcutaneous Tissue Disorders	**1 (20.0)**	**0**	**0**	**5 (100)**
Rash maculo-papular	1 (20.0)	0	0	5 (100)
Cardiac Disorders	**0**	**0**	**0**	**4 (80.0)**
Sinus tachycardia	0	0	0	4 (80.0)
Vascular Disorders	**0**	**0**	**0**	**3 (60.0)**
Hypertension	0	0	0	3 (60.0)
Metabolism and Nutrition Disorders	**2 (40.0)**	**0**	**0**	**2 (40.0)**
Decreased appetite	2 (40.0)	0	0	2 (40.0)
Hypokalaemia	2 (40.0)	0	0	2 (40.0)

Overall, **related TEAEs** were experienced by 30/38 subjects (78.9%). As expected in this patient population, related TEAEs occurred most frequently in the SOCs Blood and Lymphatic System Disorders (18 subjects, 47.4%) and Skin and Subcutaneous Tissue Disorders (16 subjects, 42.1%). The most frequently reported related TEAEs (occurring in ≥ 25% of subjects) by listed by decreasing frequency, were Febrile neutropenia and Rash maculopapular.

Study CPX-MA-1201

Among subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine in the Dose Exploration Phase, the reported TEAEs were most frequently associated with the SOCs Investigations (4 subjects, 100%), Blood and Lymphatic System Disorders (3 subjects, 75%), and Metabolism and Nutrition Disorders (3 subjects, 75%). The most frequently reported TEAEs by PT (i.e., those occurring in ≥ 75% of subjects) by decreasing frequency were Platelet count decreased, white blood cell (WBC) count decreased, Anemia, and Febrile neutropenia.

Among subjects who received CPX-351 dose of 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine in the Dose Exploration Phase, the reported TEAEs were most frequently associated with the SOCs Investigations (5 subjects, 100%), Blood and Lymphatic System Disorders (5 subjects, 100%), Skin and Subcutaneous Tissue Disorders (5 subjects, 100%), and Cardiac Disorders (4 subjects, 80%) (**Table 33**). The most frequently reported TEAEs by PT (i.e., those occurring in ≥ 75% of subjects) by decreasing frequency were Platelet count decreased, Anemia, Febrile neutropenia, Rash maculopapular, Sinus tachycardia and Neutrophil count decreased.

Among subjects who received CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine in the Expanded Phase (n = 18), the reported TEAEs were most frequently associated with the SOCs Investigations (18 subjects, 100%), Blood and Lymphatic System Disorders (18 subjects, 100%), and Skin and Subcutaneous Tissue Disorders (14 subjects, 77.8%) (**Table 33**). The most frequently reported TEAEs by PT (i.e., those occurring in ≥ 75% of subjects) by decreasing frequency were Platelet count decreased, Anemia, Febrile neutropenia, and Rash maculopapular.

Overall, among subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (regardless of whether it was in the Dose Exploration Phase or the Expanded Phase), the reported TEAEs were most frequently associated with the SOCs Investigations (22 subjects, 100%), Blood and Lymphatic System Disorders (21 subjects, 95.5%), and Skin and Subcutaneous Tissue Disorders (16 subjects, 72.7%). The most frequently reported TEAEs by PT (i.e., those occurring in ≥ 75% of subjects) by decreasing frequency were Platelet count decreased Anemia, and Febrile neutropenia.

Table 33. Study CPX-MA-1201 Treatment-emergent Adverse Events Reported in ≥ 25% of Subjects, by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Number of Subjects, n (%)			
	Dose Exploration Phase		Expanded Phase	Overall
	100 units/m^2 N = 4	134 units/m^2 N = 5	100 units/m^2 N = 18	100 units/m^2 N = 22
Subjects with any TEAE	4 (100)	5 (100)	18 (100)	22 (100)
Investigations	**4 (100)**	**5 (100)**	**18 (100)**	**22 (100)**
Platelet count decreased	4 (100)	5 (100)	17 (94.4)	21 (95.5)
White blood cell count decreased	3 (75.0)	3 (60.0)	13 (72.2)	16 (72.7)
Lymphocyte count decreased	2 (50.0)	3 (60.0)	12 (66.7)	14 (63.6)
Neutrophil count decreased	2 (50.0)	4 (80.0)	9 (50.0)	11 (50.0)
Blood bilirubin increased	1 (25.0)	0	1 (5.6)	2 (9.1)
Ejection fraction decreased	0	2 (40.0)	2 (11.1)	2 (9.1)
Electrocardiogram QT prolonged	0	1 (20.0)	2 (11.1)	2 (9.1)
Gamma-glutamyltransferase increased	1 (25.0)	0	1 (5.6)	2 (9.1)
Blood creatinine increased	1 (25.0)	0	0	1 (4.5)
Blood and Lymphatic System Disorders	**3 (75.0)**	**5 (100)**	**18 (100)**	**21 (95.5)**
Anemia	3 (75.0)	5 (100)	16 (88.9)	19 (86.4)
Febrile neutropenia	3 (75.0)	5 (100)	16 (88.9)	19 (86.4)
Skin and Subcutaneous Tissue Disorders	**2 (50.0)**	**5 (100)**	**14 (77.8)**	**16 (72.7)**
Rash maculopapular	2 (50.0)	5 (100)	14 (77.8)	16 (72.7)
Metabolism and Nutrition Disorders	**3 (75.0)**	**2 (40.0)**	**9 (50.0)**	**12 (54.5)**
Hypokalaemia	2 (50.0)	2 (40.0)	6 (33.3)	8 (36.4)
Hyperglycemia	2 (50.0)	1 (20.0)	3 (16.7)	5 (22.7)
Decreased appetite	0	2 (40.0)	4 (22.2)	4 (18.2)
Hypophosphatasemia	1 (25.0)	0	2 (11.1)	3 (13.6)
Acidosis	1 (25.0)	0	1 (5.6)	2 (9.1)
Hypomagnesaemia	1 (25.0)	0	0	1 (4.5)
Hypoalbuminemia	1 (25.0)	0	0	1 (4.5)
Hypocalcaemia	1 (25.0)	0	0	1 (4.5)
Hyponatraemia	1 (25.0)	0	0	1 (4.5)

System Organ Class Preferred Term	Number of Subjects, n (%)			
	Dose Exploration Phase		Expanded Phase	Overall
	100 units/m² N = 4	134 units/m² N = 5	100 units/m² N = 18	100 units/m² N = 22
Infections and Infestations	**2 (50.0)**	**3 (60.0)**	**5 (27.8)**	**7 (31.8)**
Lung infection	1 (25.0)	0	1 (5.6)	2 (9.1)
Skin infection	1 (25.0)	0	1 (5.6)	2 (9.1)
Sinusitis	1 (25.0)	0	0	1 (4.5)
Respiratory, Thoracic and Mediastinal Disorders	**1 (25.0)**	**1 (20.0)**	**5 (27.8)**	**6 (27.3)**
Hypoxia	1 (25.0)	0	4 (22.2)	5 (22.7)
Gastrointestinal Disorders	**2 (50.0)**	**2 (40.0)**	**2 (11.1)**	**4 (18.2)**
Stomatitis	1 (25.0)	0	1 (5.6)	2 (9.1)
Abdominal pain	1 (25.0)	1 (20.0)	0	1 (4.5)
Nausea	1 (25.0)	1 (20.0)	0	1 (4.5)
Vomiting	1 (25.0)	0	0	1 (4.5)
Vascular Disorders	**1 (25.0)**	**3 (60.0)**	**3 (16.7)**	**4 (18.2)**
Hypertension	1 (25.0)	3 (60.0)	3 (16.7)	4 (18.2)
Cardiac Disorders	**0**	**4 (80.0)**	**2 (11.1)**	**2 (9.1)**
Sinus tachycardia	0	4 (80.0)	1 (5.6)	1 (4.5)
Musculoskeletal and Connective Tissue Disorders	**1 (25.0)**	**1 (20.0)**	**1 (5.6)**	**2 (9.1)**
Osteonecrosis	1 (25.0)	0	0	1 (4.5)
Osteoporosis	1 (25.0)	0	0	1 (4.5)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Percentages of subjects are based on N.
Note: 1 unit CPX-351 = 1 mg cytarabine and 0.44 mg daunorubicin.
Note: A subjects who experienced multiple events within a SOC or PT was counted once for that class and once for the PT.
MedDRA version 21.0

Table 34. Study 1201 TEAEs in ≥ 10% of Subjects at 100 units/m2, by grades 3-5, SOC and PT

System Organ Class Preferred Term	Grade 3	Grade 4	Grade 5	Any Grade
Subjects with any TEAE	**22 (100)**	**22 (100)**	**0**	**22 (100)**
Investigations	**12 (54.5)**	**22 (100)**	**0**	**22 (100)**
Platelet count decreased	0	21 (95.5)	0	21 (95.5)
White blood cell count decreased	4 (18.2)	12 (54.5)	0	16 (72.7)
Lymphocyte count decreased	4 (18.2)	10 (45.5)	0	14 (63.6)
Neutrophil count decreased	1 (4.5)	10 (45.5)	0	11 (50.0)
Blood and Lymphatic System Disorders	**21 (95.5)**	**0**	**0**	**21 (95.5)**
Anaemia	19 (86.4)	0	0	19 (86.4)
Febrile neutropenia	19 (86.4)	0	0	19 (86.4)
Skin and Subcutaneous Tissue Disorders	**10 (45.5)**	**0**	**0**	**16 (72.7)**
Rash maculo-papular	10 (45.5)	0	0	16 (72.7)
Metabolism and Nutrition Disorders	**11 (50.0)**	**4 (18.2)**	**0**	**12 (54.5)**
Hypokalaemia	4 (18.2)	4 (18.2)	0	8 (36.4)
Hyperglycaemia	5 (22.7)	0	0	5 (22.7)
Decreased appetite	4 (18.2)	0	0	4 (18.2)
Hypophosphataemia	2 (9.1)	1 (4.5)	0	3 (13.6)
Infections and Infestations	**6 (27.3)**	**1 (4.5)**	**0**	**7 (31.8)**
Sepsis	3 (13.6)	1 (4.5)	0	4 (18.2)
Respiratory, Thoracic and Mediastinal Disorders	**3 (13.6)**	**2 (9.1)**	**0**	**6 (27.3)**
Hypoxia	2 (9.1)	2 (9.1)	0	5 (22.7)
Vascular Disorders	**3 (13.6)**	**1 (4.5)**	**0**	**4 (18.2)**
Hypertension	3 (13.6)	1 (4.5)	0	4 (18.2)

Serious adverse events/deaths/other significant events

Serious Adverse Events

Study AAML1421

Serious TEAEs (SAEs) occurred in 21/38 subjects (55.3%). The majority of SAEs were reported in the SOCs Blood and Lymphatic System Disorders and Infections and Infestations (11/38 subjects, 28.9% in each class). As expected in this subject population, and consistent with results of other studies of CPX-351, the most commonly reported SAE was febrile neutropenia (11/38 subjects, 28.9%; **Table 35**).

Table 35. Study AAML1421 Serious Treatment-emergent Adverse Events Reported in ≥ 5% of Subjects, by Preferred Term in Order of Decreasing Frequency (Safety Analysis Set)

System Organ Class **Preferred Term**	**Number of Subjects, n (%)**		
	Dose-finding Phase **N = 6**	**Efficacy Phase** **N = 32**	**Overall** **N = 38**
Subjects with any Serious TEAE	**6 (100)**	**15 (46.9)**	**21 (55.3)**
Febrile neutropenia	2 (33.3)	9 (28.1)	11 (28.9)
Rash maculopapular	0	6 (18.8)	6 (15.8)
Pyrexia	1 (16.7)	1 (3.1)	2 (5.3)
Anorectal infection	1 (16.7)	0	1 (2.6)
Death	1 (16.7)	0	1 (2.6)
Dysphagia	1 (16.7)	0	1 (2.6)
Ejection fraction decreased	1 (16.7)	0	1 (2.6)
Escherichia infection	1 (16.7)	0	1 (2.6)
Hemiparesis	1 (16.7)	0	1 (2.6)

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Dose-finding Phase N = 6	Efficacy Phase N = 32	Overall N = 38
Hypoxia	1 (16.7)	0	1 (2.6)
Sepsis	1 (16.7)	0	1 (2.6)
Septic shock	1 (16.7)	0	1 (2.6)
Staphylococcal infection	1 (16.7)	0	1 (2.6)
Streptococcus test positive	1 (16.7)	0	1 (2.6)

Abbreviations: CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event. Note: A TEAE was defined as any event with onset date on or after the treatment start date in eligibility CRF up to 30 days after last reporting period end date, or any ongoing event that worsened in severity after the date of the first dose of study drug up to and including 30 days after last reporting period end date. Note: Multiple entries for an individual subject under each PT are only counted once. Note: Subjects received Cycle 1 CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine in Dose-finding Phase and Efficacy Phase. Note: This table displays TEAEs with onset dates in Cycle 1, Cycle 2, or Follow-up. Note: Percentages of subjects are based on N. Note: MedDRA version 21.0

An examination of SAEs with onset dates during Cycle 1 only, and with onset dates during Cycle 1 and Cycle 2 only, that were reported in ≥ 5% of subjects by SOC and PT revealed a display similar to what is presented in Table 5.5.5.

Treatment-related SAEs occurred in 20/38 subjects (52.6%). The majority of treatment-related SAEs were reported in the SOCs Blood and Lymphatic System Disorders (11/38 subjects, 28.9%) and Infections and Infestations (9/38 subjects, 23.7%). The most commonly reported treatment-related SAE by PT was Febrile neutropenia (11/38 subjects, 28.9%; **Table 36**).

Table 36. Study AAML1421 Related Serious Treatment-emergent Adverse Events Reported in ≥ 5% of Subjects, by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Number of Subjects, n (%)		
	Dose-finding Phase N = 6	Efficacy Phase N = 32	Overall N = 38
Subjects with any Related Serious TEAE	**5 (83.3)**	**15 (46.9)**	**20 (52.6)**
Blood and Lymphatic System Disorders	**2 (33.3)**	**9 (28.1)**	**11 (28.9)**
Febrile neutropenia	2 (33.3)	9 (28.1)	11 (28.9)
Infections and Infestations	**4 (66.7)**	**5 (15.6)**	**9 (23.7)**
Anorectal infection	1 (16.7)	0	1 (2.6)
Escherichia infection	1 (16.7)	0	1 (2.6)
Sepsis	1 (16.7)	0	1 (2.6)
Staphylococcal infection	1 (16.7)	0	1 (2.6)
Skin and Subcutaneous Tissue Disorders	**0**	**6 (18.8)**	**6 (15.8)**
Rash maculopapular	0	6 (18.8)	6 (15.8)
Investigations	**2 (33.3)**	**2 (6.3)**	**4 (10.5)**
Ejection fraction decreased	1 (16.7)	0	1 (2.6)
Streptococcus test positive	1 (16.7)	0	1 (2.6)
Gastrointestinal disorders	**0**	**3 (9.4)**	**3 (7.9)**
Colitis	0	2 (6.3)	2 (5.3)
General disorders and administration site conditions	**0**	**2 (6.3)**	**2 (5.3)**
Metabolism and nutrition disorders	**0**	**2 (6.3)**	**2 (5.3)**

Abbreviations: CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event. Note: A TEAE was defined as any event with onset date on or after the treatment start date in eligibility CRF up to 30 days after last reporting period end date, or any ongoing event that worsened in severity after the date of

the first dose of study drug up to and including 30 days after last reporting period end date. Note: Multiple entries for an individual subject under each SOC / PT are only counted once. Note: Subjects received Cycle 1 CPX-351 dose of 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine treatment in Dose-finding Phase and Efficacy Phase. Note: Percentages of subjects are based on N. Note: MedDRA version 21.0

An examination of treatment-related SAEs with onset dates during Cycle 1 only, and with onset dates during Cycle 1 and Cycle 2 only, that were reported in ≥ 5% of subjects by SOC and PT revealed a display similar to the presentation in **Table 36**.

Study CPX-MA-1201

Overall, among subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (regardless of whether it was in the Dose Exploration Phase or the Expanded Phase), 18/22 subjects (81.8%) reported SAEs (**Table 37**). The majority of SAEs were reported in the SOCs Blood and Lymphatic System Disorders (17/22 subjects, 77.3%) and Infections and Infestations (6/22 subjects, 27.3%). The most commonly reported SAE was Febrile neutropenia (17/22 subjects, 77.3%).

Table 37. Study CPX-MA-1201 Serious Treatment-emergent Adverse Events by Preferred Term in Order of Decreasing Frequency (Safety Analysis Set)

	Number of Subjects, n (%)			
	Dose Exploration Phase		**Expanded Phase**	**Overall**
Preferred Term	**100 units/m^2 N = 4**	**134 units/m^2 N = 5**	**100 units/m^2 N = 18**	**100 units/m^2 N = 22**
Subjects with any Serious TEAEs	2 (50.0)	5 (100)	16 (88.9)	18 (81.8)
Febrile neutropenia	1 (25.0)	4 (80.0)	16 (88.9)	17 (77.3)
Hypoxia	1 (25.0)	0	3 (16.7)	4 (18.2)
Sepsis	0	1 (20.0)	3 (16.7)	3 (13.6)
Hypertension	0	0	2 (11.1)	2 (9.1)
Lung infection	1 (25.0)	0	1 (5.6)	2 (9.1)
Stridor	0	0	2 (11.1)	2 (9.1)
Acidosis	0	0	1 (5.6)	1 (4.5)
Glaucoma	0	0	1 (5.6)	1 (4.5)
Infection	0	0	1 (5.6)	1 (4.5)
Pain	0	1 (20.0)	1 (5.6)	1 (4.5)
Posterior reversible encephalopathy syndrome	0	0	1 (5.6)	1 (4.5)
Pulmonary oedema	0	0	1 (5.6)	1 (4.5)
Seizure	0	0	1 (5.6)	1 (4.5)
Skin infection	0	0	1 (5.6)	1 (4.5)
Bacteraemia	0	1 (20.0)	0	0
Cellulitis	0	1 (20.0)	0	0
Colitis	0	1 (20.0)	0	0
Headache	0	1 (20.0)	0	0
Nausea	0	1 (20.0)	0	0
Osteomyelitis	0	1 (20.0)	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Percentages are based on N.
Note: 1 unit CPX-351 = 1 mg cytarabine and 0.44 mg daunorubicin.
Note: A TEAE was defined as any event with onset date on or after the first dose of study drug until 30 days after the last dose, or any ongoing event that worsened in severity after the date of the first dose of study drug up to and including 30 days after the last dose of

study drug. TEAE severity was graded by the investigator as Grade 1, 2, 3, 4, or 5. Maximum grade was captured in the case report form.
Note: A subject who experienced multiple events within an SOC or PT was counted once for that class and once for the PT.
Note: MedDRA version 21.0

Deaths

Study AAML1421

No deaths occurred while subjects received protocol therapy. A total of 12 deaths occurred during the protocol-defined Follow-up Phase (i.e., after subjects had completed the Treatment Phase of the study); none of these were considered related to protocol therapy. A total of 8 deaths were due to progressive disease and 4 were due to other causes. Half of the deaths (6/12 deaths) were reported within the 6-month Follow-up Period (FU 1), 4 deaths were reported within the 1-year FU 2, and death was reported for 1 subject each at the 2-year (FU 3) and 3-year (FU 4) periods.

Study CPX-MA-1201

No deaths occurred while subjects received protocol therapy. A total of 10 subjects died during the protocol-defined follow-up period and were due to disease progression.

Adverse Events of Special Interest

Study AAML1421 and study CPX MA 1201: there were no AEs of special interest (AESIs) prespecified for the RR-AML paediatric studies.

Laboratory findings

According to the MAH, routine laboratory monitoring of haematology, electrolytes, blood chemistry and urine and regular assessments of vital signs and physical condition were performed by Investigators for monitoring the safety of all subjects but were not collected as part of the study data. These routine laboratory assessments were recorded in the subjects' medical record. AEs identified from laboratory parameters were to be reported on the AE CRF. Therefore, routine lab results are not included or discussed in the CSRs.

Hematology

Transfusions of platelets and red blood cells can ameliorate the worst consequences of thrombocytopenia and anaemia in most, but not all cases; during the CPX-351 clinical program transfusions were administered frequently.

Absolute Neutrophil Count

Study AAML1421

Although ANC values were not provided in the datasets for AAML1421, responses were verified based on data available in the CRF, including marrow blast percentage and threshold levels for ANC and platelet counts at the end of induction (ANC $\geq 1 \times 10^9$/L versus $< 1 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L versus $< 100 \times 10^9$/L, respectively).

Additionally, the time to peripheral ANC recovery is as follows: at the end of Cycle 1, the mean (SD) time to ANC recovery overall among subjects with CR or CRp was 44.3 (7.21) days. The mean time to ANC recovery was similar for subjects participating in the Dose-finding Phase and the Efficacy Phase.

At the end of Cycle 2, the mean (SD) time to ANC recovery overall among subjects with CR or CRp was 74.2 (11.16) days.

Study CPX-MA-1201

Among subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (regardless of whether it was in the Dose Exploration Phase or the Expanded Phase), most subjects had Grade 4 abnormal ANC levels. The exceptions included 1 subject with Grade 0 ANC levels (within normal limits) at baseline and during treatment, and 2 subjects with abnormal Grade 4 ANC levels at baseline who improved to Grade 2 and Grade 3 during treatment.

During treatment, among subjects who received CPX-351 at a dose of 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine in the Dose Exploration Phase, all subjects had Grade 4 abnormal ANC levels.

Platelet Count

Study AAML1421

Although laboratory values for AAML1421 are not presented in the datasets, of note, hematologic DLTs were defined as failure to recover a peripheral ANC > 500/µL and non-transfusion dependent platelet count > 20,000/µL due to documented bone marrow aplasia/hypoplasia (that is, not due to malignant infiltration) for ≥ 50 days from the start of the therapeutic cycle. Failure to recover peripheral counts due to disease involvement of the bone marrow were not considered dose-limiting.

In the Efficacy Phase, if after Cycle 1 a subject had a hypoplastic bone marrow for ≥ 60 days and failure to recover a peripheral ANC > 500/µL and a non-transfusion dependent platelet count > 20,000/µL not due to malignant infiltration or severe infection (defined as ≥ Grade 3 infection), they were considered a treatment failure and went off protocol therapy.

Study CPX-MA-1201

Among subjects who received a CPX-351 dose of 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine (regardless of whether it was in the Dose Exploration Phase or the Expanded Phase), 6 subjects had normal platelet levels at baseline. Three subjects had Grade 4 abnormal platelet levels at baseline, and all but 1 of these subjects improved to Grade 3 during study treatment.

During treatment, among subjects who received a CPX-351 dose of 59 mg/m^2 daunorubicin and 134 mg/m^2 cytarabine in the Dose Exploration Phase, most subjects had ≤ Grade 2 abnormal platelet levels at baseline. During study treatment, platelet levels remained relatively stable for most subjects, with the exception of 1 subject who had Grade 1 abnormal platelet levels at baseline and had Grade 3 abnormal platelet levels during treatment.

Hemoglobin

Study AAML1421 and Study CPX-MA-1201

Regular assessments of haemoglobin were performed by Investigators to monitor subject safety, but were not collected as part of the study data. These routine assessments were recorded in the subject medical records. Adverse Events identified from assessments of haemoglobin were to be reported on the AE CRF but were not reported in the laboratory datasets.

Clinical Chemistry

Serum Creatinine

Study AAML1421 and Study CPX-MA-1201

Serum creatinine levels were performed by Investigators to monitor the safety of all subjects but were not collected as part of the study data. These routine laboratory assessments were recorded in the subjects' medical records. Adverse event identified from the assessments of serum creatinine were to be reported on the AE CRF. Therefore, these results are not included or discussed for Study AAML1421 and Study CPX-MA-1201.

Serum Bilirubin

Study AAML1421 and Study CPX-MA-1201

Serum bilirubin levels were performed by Investigators for monitoring the safety of all subjects, but were not collected as part of the study datasets for AAML1421 and Study CPX-MA-1201. These routine laboratory assessments were recorded in the subjects' medical record. Adverse Events identified from assessments of serum bilirubin were to be reported on the AE CRF. Therefore, these results are not included or discussed for these studies.

Urinalysis

Urinalysis was conducted in each of the clinical trials within the CPX-351 clinical development program. No remarkable findings of any clinical concern were reported.

Serum Copper

Since CPX-351 contains copper encapsulated in the liposome, which acts as a chelating agent to maintain a slow release rate for daunorubicin, subjects were monitored for serum copper concentrations during each of the clinical studies conducted in the CPX-351 development program.

Study AAML1421

Serum copper values were not reported for AAML1421.

Study CPX-MA-1201

Serum copper levels increased from Baseline by Day 5 up to a mean of 800 µg/dL. Of note, the upper limit of quantitation of serum copper concentration by the clinical laboratory assay was 800 µg/dL. Values ≥ 800 µg/dL were reported as 800 µg/dL. Serum copper levels generally returned to baseline levels by the completion of course 1.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Sign Data

For the paediatric studies AAML1421 and CPX-MA-1201, regular assessments of vital signs and physical condition were performed by Investigators for monitoring subject safety, but were not collected as part of the study data. These routine assessments were recorded in the subjects' medical record. Adverse events identified from assessments of vital signs and physical condition were to be reported on the AE CRF. Therefore, these results were not available for inclusion or discussion in this submission.

Electrocardiogram Data

Inclusion criteria in both studies required adequate cardiac function, defined as: Shortening fraction of ≥ 27% by echocardiogram, or Ejection fraction of ≥ 50% by radionuclide angiogram or echocardiogram. Study 1421 additionally required a Bazett's corrected QT (QTcB) interval < 500 msecs.

Study AAML1421

Measures of left ventricular ejection fraction (LVEF) and left ventricular shortening Fraction (LVSF) over time were assessed by ECHO. In addition, QT interval was assessed by ECG over 2 cycles of therapy and follow-up. The highest corrected QT interval (QTc) was summarized. Measures of cardiac function revealed limited impact of CPX-351 during the course of the study. Mean and median LVSF and LVEF values assessed during ECHO remained near or within normal limits.

Study AAML1421 Corrected QT Interval

Treatment with CPX-351 did not significantly impact QTc intervals during the course of the study. While a trend towards increasing mean and median QTcs was seen through Follow-up 1, values returned to baseline (study entry) by the time of Follow-up. Results of mean and median QTcs at Follow-up 3 and Follow-up 4 should be interpreted with caution due to the low number of subjects with ECG evaluations.

There were 7 events of QTc prolongation in the Cycle 1 reporting period; all were Grade 1, and 3/7 were related to study medication. One subject recorded a corrected QT > 500 msec during Follow-up 1. The event was reported as an AE (CTCAE Grade 3) with the PT Electrocardiogram QT prolonged. Eight additional subjects recorded a corrected QT ≥ 480 msec and 11/38 subjects overall (28.9%) experienced TEAEs with the PT Electrocardiogram QT prolonged. None of these 11 events was ≥ Grade 3.

Of note, subjects were on concomitant therapy with other drugs known to prolong the QT interval (e.g., azole antifungal prophylaxis). Three events (2 unrelated and 1 related) occurred during concurrent infection events (pneumonia in 2 subjects and mucosal infection in 1 subject).

Table 38. Cardiac Evaluation Summary: Highest Corrected QT Interval Over Time (Safety Analysis Set)

	Proportion of Subjects with ECG Evaluated, n (%)	**n**	**Mean (SD)**	**Median**	**Min, Max**
Study Entry	35 (92.1)	35	416.8 (34.38)	424.0	306, 456
Cycle 1	33 (86.8)	33	426.4 (32.69)	435.0	328, 477
Cycle 2	20 (52.6)	20	444.0 (25.08)	441.0	405, 494
Follow-up 1 (6 mo)	20 (52.6)	20	444.8 (38.94)	440.0	389, 524
Follow-up 2 (1 yr)	9 (23.7)	9	424.8 (49.80)	418.0	340, 499
Follow-up 3 (2 yr)	2 (5.3)	2	407.0 (7.07)	407.0	402, 412
Follow-up 4 (3 yr)	1 (2.6)	1	497.0 (NC)	497.0	497, 497

Abbreviations: ECG = electrocardiogram; Max = maximum; Min = minimum; mo = month; NC = not calculated; SD = standard deviation; yr = year.

Safety in special populations

Intrinsic Factors

Exposure-response in Pediatrics and Young Adults

An exposure-response (ER) analysis of safety was performed to include the paediatric population based on data from a total of 46 (18.5%) paediatric subjects (1 to 17 years old) from Study CPX-MA-1201 and Study AAML1421 and 204 (81.5%) adults (≥ 18 years) from Study 101, Study 206, and Study 301. Subjects were dosed with either 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine or 59 mg/m^2 daunorubicin and 135 mg/m^2 cytarabine. Exposure-response analysis in this combined adult and paediatric

population determined the impact of drug exposure on the probability of the most frequent TEAEs reported which included the PT Neutropenia reported in 141/178 (79.2%) subjects with the "blood and lymphatic system disorders" SOC and the PT Rash reported in 79/203 (38.9%) of subjects with "skin and subcutaneous tissue disorders" SOC. The effect of cytarabine maximum concentration (C_{max}) or area under the concentration-time curve 0 to 48 (AUC_{0-48}) on the probability of neutropenia were statistically significant (p = 0.0011 and p = 0.0354, respectively). The odds ratio for the C_{max} of cytarabine was 1.015, which suggests that the odds of response increased by approximately 1.5% for each 1 unit increment of cytarabine C_{max} (i.e. 1 µg/mL). The C_{max} and AUC_{0-48} of cytarabine was also a statistically significant predictor of the probability of rash (p = 0.0092 and p = 0.0354, respectively), with and odds ratio of 1.012.

These results suggest that both the C_{max} or AUC_{0-48} of cytarabine are predicative of neutropenia and rash. Similar to what observed in previous ER analysis for safety, when assessing the probability of any Grade 3 to 5 TEAE in the paediatric population only (Study CPX-MA-1201 and Study AAML1421), no apparent ER relationship was observed. Additionally, in the paediatric population, no statistically significant effect of cytarabine C_{max} was observed on the time to recovery of ANC or time to platelet recovery.

Use in Pregnancy and Lactation

No clinical data are available regarding the safety of CPX-351 during pregnancy or lactation.
Women of childbearing potential should avoid becoming pregnant while receiving CPX-351. Women of childbearing potential should use effective contraception while they or their male partner undergo treatment. Women of childbearing potential should not receive treatment until pregnancy is excluded.

Women of childbearing potential should undergo pregnancy testing before initiation of CPX-351. Men with sexual partners of reproductive potential, and women should use effective contraception during treatment and for 6 months following the last dose of CPX-351.

Extrinsic Factors

Specific data extrinsic factors were not collected during clinical studies of CPX-351. A relationship between these factors and CPX-351 exposure is unknown.

Safety related to drug-drug interactions and other interactions

No formal assessments of pharmacokinetic drug-drug interactions between CPX-351 and other agents have been conducted.

Discontinuation due to adverse events

In *study AAML1421*, there were no TEAEs leading to discontinuation.

In *study CPX-MA-1201,* AE data was not collected to enable reporting of discontinuations due to TEAEs.

Post marketing experience

Paediatric and young adult patients

None

Adults

Estimated cumulative exposure in ongoing and completed Jazz Pharmaceuticals, Inc.-sponsored interventional clinical trials is Vyxeos (CPX-351) n = 475 through 02 August 2020. Vyxeos Periodic Benefit-risk Evaluation Report (PBRER), dated 06 October 2020, is the 6th semi-annual report submitted to the US and the 4th PBRER (PSUR) submitted to the EU. It summarizes the cumulative safety profile from clinical trials and post marketing data covering the period 03 February 2020 through 02 August 2020 (MAA EMEA/H/C/004282 SN-0039, submitted 09 October 2020). The PBRER details benefit-risk information for Vyxeos including a cumulative and interval summary tabulation of serious and non-serious adverse reactions from post marketing data sources.

As of the current PBRER (dated 03 April 2020), no actions (e.g., failure to obtain or apply for marketing approval renewal, withdrawal or suspension of a marketing approval, or suspension of supply) by Jazz Pharmaceuticals, Inc. due to a safety reason have been taken.

Literature search

Given that the cytarabine and daunorubicin components of CPX-351 have been marketed for over 40 years, a literature search (March 2017 using EMBASE, MEDLINE; via Embase.com) was conducted by the MAH to summarize the known safety contributions of the individual agents. The following summarizes specific areas of literature search regarding known safety effects of cytarabine and daunorubicin.

Myelosuppression

Administration of anthracyclines is associated with significant bone marrow suppression, frequent infections (as a result of neutropenia), increased risk for bleeding events (resulting from thrombocytopenia) (Atallah et el 2007) (Moreau et al. 2009) (Gupta et al. 2010).

Cardiotoxicity

Administration of anthracyclines is associated with cardiac toxicity (specifically associated with higher doses of daunorubicin administered for longer durations) (Volkova, 2011), (Von Hoff, 1979). Total cumulative doses of greater than 550mg/m2 have been associated with an increased incidence of drug induced congestive heart failure. This limit appears lower in patients who received radiation therapy to the mediastinum.

Total cumulative doses of daunorubicin greater than 550mg/m2 have been associated with an increased incidence of drug induced congestive heart failure (Tan 2015). Prior therapy with anthracyclines, pre-existing cardiac disease, previous mediastinal radiotherapy or concomitant use of cardiotoxic drugs may increase the risk of daunorubicin induced cardiac toxicity. (Volkova, 2011; Menna 2012).

The use of adjuvant chemotherapeutic agents known to be cardio-toxic increases the risk of heart failure among radiation-treated patients (Senkus-Konefka and Jasseem 2007) History of chest irradiation is a cardiac risk factor (Anderson and. Sawyer 2008).

Risk factors for cardiotoxicity include cumulative dose and concomitant treatment with cyclophosphamide, trastuzumab or paclitaxel (Volkova, 2011).

Myocarditis

Rare instances of pericarditis-myocarditis, not dose-related, can occur with the use of anthracyclines. Clinically, early cardiac side effects are typically reversible and self-limiting and include dysrhythmia, repolarization changes in the electrocardiogram, pericarditis, and less frequently myocarditis (Senkus and Jassem 2011). These complications do not preclude further anthracycline use (Suter and Ewer 2013).

Renal and Hepatic Impairment

Significant hepatic or renal impairment may increase the risk of toxicity associated with cytarabine and daunorubicin. Renal insufficiency is a risk factor in the development of cerebral toxicity during cytarabine treatment (Hasle 1990) (Damon et al. 1989). Anthracyclines are primarily metabolized by the liver with approximately 50% excreted via bile (Barker et al. 2016).

Hyperuricemia

Metabolic abnormalities characteristic of Tumour lysis syndrome (TLS) include abnormally high serum uric acid levels (hyperuricemia). TLS typically occurs after the initiation of anticancer therapies, including cytotoxic drugs, biological agents, corticosteroids, hormones, and radiation therapy, in patients with hematologic malignancies or solid tumours that are highly treatment sensitive. Daunorubicin has a nephrotoxic potential (Mughal et al. 2010)

Tissue Necrosis

Anthracyclines can persist in tissues for weeks or even months after extravasation. The local area of extravasation is at high risk of infection, because of both the local necrosis and in general by the impaired immunological state of most patients receiving this kind of treatment. For significant anthracycline extravasations, there is a high risk of ulceration and a possible need for surgery (Langer et al. 2009, Jordan et al. 2009)

Hypersensitivity and Rash

Hand-foot syndrome (palmoplantar erythrodysesthesia) may result from liposomal anthracyclines (Reyes et al. 2014)). Studies show that liposomal formulations of anticancer drugs are less toxic than the non-encapsulated formulations, although some liposome-specific adverse effects such as various skin reactions, and also hypersensitivity reactions have been reported (Slingerland et al. 2012).

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine (Cytarabine PI; Daunorubicin PI).

Gastrointestinal events

Administration of anthracyclines is associated with GI side effects (such as nausea, vomiting and diarrhoea). Chemotherapy-Induced Nausea and Vomiting (Hesketh 2008; Peric and Reeves, 2015.)

1.7.1. Discussion on clinical safety

In support of this variation and safety, the MAH submitted two paediatric studies. Study AAML1421 was a phase 1/2, open label, single-arm, dose escalating study of CPX-351 followed by fludarabine, cytarabine and filgrastim (FLAG) in 38 paediatric and young adult patients (age range from 1 to 21 years) with RR-AML; study CPX-MA-1201 was a phase 1, open label, single arm, dose escalating, pilot study of CPX-351 in paediatric and young adult patients (age range from 1 to 19 years), with RR-AML or acute lymphocytic leukaemia (ALL).

In general, the safety findings in paediatric studies were relatively consistent with those observed in adult patients. Within serious and serious related TEAEs, febrile neutropenia occurred at a significantly higher rate in both paediatric studies than in the adult studies: in study 1421, frequency was 28.9%, all were considered related, whereas in the pooled adult population, frequency was 10.1%, considering induction only 5.3%. The MAH further clarified, that no new or unexpected safety findings were evident from the

analysis of the paediatric data compared to safety data obtained from adult studies and the post marketing experience.

Increasing the intensity of induction chemotherapy to enhance overall survival often comes at the cost of high treatment-related toxicity. As such, mortality rates following initiation of therapy are considered important measures of SAEs. Specifically, mortality rates at day 30 and day 60 are generally considered as markers of early death associated with treatment.

No deaths occurred while subjects received protocol therapy. In study AAML1421 total of 12 deaths occurred during the protocol-defined Follow-up Phase (i.e., after subjects had completed the Treatment Phase of the study); none of these were judged to be related to protocol therapy. A total of 8 deaths were due to progressive disease and 4 were due to other causes. Half of the deaths (6/12 deaths) were reported within the 6-month Follow-up Period, 4 deaths were reported within the 1 year, and death was reported for 1 subject each at the 2 year and 3-year periods.

The MAH clarified that all deaths appeared not to be related to treatment with Vyxeos. Clustering on any certain age strata was not clearly evident.

According to the MAH, in study AAML1421, there were no TEAEs leading to discontinuation and such data was not accrued in the pilot study.

Administration of anthracyclines is associated with cardiac toxicity, specifically with higher doses of daunorubicin administered for longer period of time. Rare instances of pericarditis-myocarditis, not dose-related, can also occur. It can also be associated with reduction in left ventricular ejection fraction (LVEF) and congestive heart failure. Acknowledging the inherent high morbidity of the patients under study, the results of ECHO and ECG measurements appeared not to cause any specific, major concerns in this limited study sample (study AAML1421). ECG and QT results suggest only a minor effect on the QTc interval with 1 QT prolongation >500ms (grade 3) at the 135 U/m² dose of CPX-351 in paediatrics, which overall confirms conclusions in adults. Regarding cardiac function it appeared that LVSF remained stable, whereas LVEF appeared to decrease slightly from BL. Nearly 25% of patients (8 of 35) experienced reduced LVEF $\leq$ 50% during the study. However, follow-up data are from 1-2 patients only. 1 SAE of decreased ejection fraction (36%, grade 3) was reported as DLT during cycle 1. Overall, frequency of cardiac/QT-related TEAEs was higher in both paediatric studies than in adult studies. It is deemed appropriate to explore exposure-response for cardiotoxicity-related TEAEs, also considering cumulative doses. Further, for study 1201 cardiac no ECG and ECHO results are available.

Furthermore, drug-induced prolongation of the QT/QTc interval is usually asymptomatic, and an increased rate of certain adverse events in patients taking an investigational agent can signal potential proarrhythmic effects. In study AAML1421 one event was reported as an TEAE (CTCAE Grade 3) with the PT Electrocardiogram QT prolonged. Eight additional subjects recorded a corrected QT $\geq$ 480 msec and 11/38 subjects overall (28.9%) experienced TEAEs of QT prolongation. None of these 11 events was $\geq$ Grade 3. Firm conclusions on the basis of the results, including the incidences of AE/SAE on cardiac safety, cannot, however, be made. Confounding by concomitant therapy with other drugs known to prolong the QT interval may, according to the MAH, also be present.

Available evidence of the cardiotoxic potential of Vyxeos liposomal has been reflected in the product information which states that cardiac disorders (including sinus tachycardia, QT prolongation and ejection fraction decreased) were observed in studies in anthracycline pre-treated children with relapsed or refractory AML treated with a single induction cycle (Cycle 1) of Vyxeos liposomal. Several other long-term studies of treatment with anthracycline/ anthracenedione in children suggest that congestive cardiomyopathies with a latency of many years may occur

Patients with AML or ALL suffer from impaired hematopoietic function and often present with anaemia, thrombocytopenia and abnormal neutrophil counts prior to receiving treatment. Due to the nature of the

disease, treatment-related myelosuppression is an important safety concern monitored by evaluation of laboratory parameters including absolute neutrophil count (ANC) and platelet counts. Reductions in ANC and platelet production directly influence the frequency of acute myelosuppression-related downstream AEs, such as susceptibility to infections and increased risk of bleeding/anaemia. Furthermore, due to the nature of the disease and intensive treatment required, monitoring renal and hepatic function enables optimization of treatment and clinical management of patients with AML.

The impact of intrinsic factors including demographic subgroups of age, race, gender, renal impairment and hepatic impairment on the safety of CPX-351 were not evaluated in the paediatric patients. Also, any possible relationship between extrinsic factors and CPX 351 exposure is unknown, as specific data were not collected during the clinical studies. No data on transfusions were provided other than that they were frequent. Furthermore, there were no AEs of special interest (AESIs) prespecified for the RR-AML paediatric studies.

Further uncertainties remain with respect the safety of Vyxeos liposomal in the treatment of paediatric and young adult patients with RR-AML. Even acknowledging the orphan status of Vyxeos liposomal, the overall numbers of patients under study are small and derive mainly from a sole phase 1/2 study AAML1421. The open label, single arm design also limits the interpretation of the safety results. In addition, the long-term safety data derives mainly from this single, open label, single arm, phase 1/2 study and are, to date, partly pending, as the LTE of this study is still ongoing. The MAH clarified that the current CSR is to be considered as the final one. A sentence on lack of long-term data especially on cardiac safety has been added to the PI and is acceptable. The requested text on the lack of overall paediatric safety data beyond the duration of the provided clinical trials has also been added, on request.

The effects of Vyxeos liposomal on growth and maturation was not evaluated in the submitted studies. A sentence on the lack of these data has been added to the SmPC.

The number of reported AEs and SAEs is high; however, high toxicity can be expected in the target population given the known consequences of intensive chemotherapy in a heavily pre-treated patient population. Based on the provided data from these 2 investigator-initiated trials, the overall clinical safety of CPX 351 seems tolerable and acceptable for the treatment of paediatric patients > 1 years with R/R AML, notwithstanding the limitations of the provided safety data. It is advantageous that both drug substances in non-liposomal intravenous formulations are known and used for years in the treatment of paediatric AML. Safety concerns pertains also to the question of anthracycline pre-treatment and maximal cumulative dose of daunorubicin to prevent long-term cardiotoxicity. Studies excluded patients above certain pre-dose thresholds, but it is unclear whether current recommendations for upper limits were followed.

It is, furthermore, noted that at the time of the original MAA the data submitted was not considered sufficient for the indication of adult RR-AML. This inherently means that there is no adequate trial for Vyxeos liposomal with a positive benefit-risk in the treatment of adults with RR-AML. Text on this issue has been adequately added to the SmPC.

Some question concerning safety were raised based on the original documentation submitted to support the extension of the Vyxeos indication to paediatric and young adult patients with RR-AML. The MAH chose mostly not to answer these questions on the basis that it was no longer pursuing the extension of the indication and these data are thus not needed.

The current paediatric safety data concern a different indication compared to the approved adult indication. However, relevant safety information has been reflected in Sections 4.4 and 4.8 of the SmPC.

On the basis of the submitted data on the safety profile of Vyxeos liposomal in the treatment of RR-AML in paediatric patients no major objections concerning safety were raised. All open safety issues, OCs,

have been resolved; no unresolved issues remain thus, this variation is considered approvable from the safety point of view.

1.7.2. Conclusions on clinical safety

The safety profile of Vyxeos liposomal in the paediatric pre-treated R/R AML population, appeared, in general, to be comparable to that of the treatment-naïve adult population. There are no outstanding concerns regrading the safety of the product from the available data and thus the variation of the marketing authorisation for Vyxeos liposomal to update sections 4.8, 5.1 and 5.2 of the SmPC is considered from a safety point of view, approvable.

1.7.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.8. Risk management plan

The MAH submitted an updated RMP version 1.1 with this application. As the new proposed indication was withdrawn the submitted updated RMP is no longer applicable.

1.9. Update of the Product information

As a consequence of this variation, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2. Benefit-Risk Balance

2.1.1. Disease or condition

The proposed indication was initially for the treatment of relapsed or refractory AML in paediatric and young adult patients aged 1 to 21 years old. The aim of treatment for patients with relapsed AML is to prolong survival.

2.1.2. Available therapies and unmet medical need

Long-term survival rates of pediatric AML patients are currently 70% or even higher. Current first line treatment strategy that includes four to five courses of intensive myelosuppressive chemotherapy, mainly based on anthracyclines and cytarabine with or without (HSCT).

Regarding novel agents, treatment modalities, targeted therapies and drugs such as venetoclax, monoclonal antibodies, and cellular therapies are investigated in AML.

However, up to 40% of the children the AML relapses, with a probability of long-term survival of approximately 40%. These poor outcomes indicate the need for improved treatment, including innovative drugs and treatment modalities.

For patients who relapse, or are refractory to first-line therapy there is a limited number of effective agents available. For the reinduction therapy, several agents have used, including re-introduction of anthracyclines and cytarabine. Other possibilities include use of mitoxantrone (alone or in combination therapy), clofarabine (alone or in combination therapy) and FLAG (alone or in combination therapy).

Optimal treatment for paediatric relapsed AML is not well defined, regarding optimal chemotherapy, the need for allo-HSCT, the timing of an allo-HSCT and risk group stratified treatment based on prognostic factors. However, allo-HSCT in second complete remission (CR2) after reinduction chemotherapy is associated with better outcome than chemotherapy only, and once paediatric patient relapses, working toward an allo-HSCT is currently a rule.

Relapsed paediatric AML carries a poor prognosis and represents an unmet medical need.

2.1.3. Main clinical studies

Study AAML1421 was a phase 1/2, multicenter study of CPX-351 for children with AML in first relapse, conducted and sponsored by Children's Oncology Group (COG). The primary objectives of this study were to determine a recommended phase 2 dose (RP2D) and the toxicities associated with CPX-351 in pediatric and young adult patients with relapsed/refractory AML and to estimate the response rate (complete remission [CR] + complete remission with partial platelet recovery [CRp]) after CPX-351 (Cycle 1) followed by fludarabine/cytarabine/G-CSF (FLAG; Cycle 2) in children with AML in first relapse. The MAH was not involved in the study conduct, but received the data from the Sponsors and summarised the results of the study for the purposes of current regulatory submission.

This study comprised 2 phases: a dose-finding and an efficacy phase and altogether 38 patients were included into the study (6 in the dose-finding and 32 in the efficacy phase). In both phases of the study, Cycle 1 treatment consisted of 2 doses of intrathecal (IT) cytarabine (age-based dosing) along with CPX-351 administered IV over 90 minutes on Days 1, 3, and 5. Cycle 2 of therapy consisted of FLAG. All patients were treated at the same CPX-351 dose, namely 135 units/m2/dose (i.e. 59 mg/m2 daunorubicin and 135 mg/m2 cytarabine).

2.2. Favourable effects (study AAML1421)

The primary efficacy endpoint displayed an overall response rate (CR + CRp) of 68% and the best response rate (CR + CRp + CRi) of 81% after CPX-351 (cycle 1) followed by FLAG (cycle 2).

The secondary efficacy endpoint displayed a response rate (CR + CRp) of 43.2% and the best response rate (CR + CRp + CRi) of 76% after CPX-351 (cycle 1).

The median OS was 32.5 months for all 37 efficacy evaluable patients and 10.1 months for the 7 non-responders, respectively. In all 26/37 subjects (70.3%) were alive at the time of analysis, or were censored before or at the time of analysis.

2.3. Uncertainties and limitations about favourable effects

The efficacy claims are based on a single, uncontrolled, phase I/II pivotal study.

Because of the unconventional method to calculate the number of responders (both with regard to primary and secondary efficacy endpoint) used in this SAT, the MAH should provide the response rate as a simple proportion of responders with the corresponding Clopper-Pearson confidence interval.

Due to the large heterogeneity of the targeted population and the low sample size being included into the single pivotal study (n=37), uncertainties regarding efficacy in subgroups of clinically relevant prognostic value remain due to incomplete information provided:

- age groups '≥1 to <2' vs '≥2 to <12' vs '≥12 to <18'
- relapsed vs refractory AML setting
- prior allogeneic HSCT status
- prior therapy with cytarabine/daunorubicin
- time-to-relapse

CR rate and CR/CRi/CRp rate are not considered established or validated surrogate markers for OS in AML. The clinical relevance of CR/CRp/CRi is based on the fact that blast reduction is a prerequisite of a HSCT after (re-)induction therapy, being the only therapeutic option with curative intent in a high-risk AML setting. Data on patients proceeding to a HSCT is incomplete, and follow-up data on OS was not provided, and therefore it was not possible to assess the clinical relevance of the reported outcomes.

2.4. Unfavourable effects

In study AAML1421, the majority of subjects experienced TEAEs and related TEAEs during the study. More than half of subjects experienced serious TEAEs, and related serious TEAEs. The majority of subjects (89.5%) experienced events categorized as ≥ Grade 3, with 4 subjects (10.5%) experiencing Grade 4 TEAEs, and 1 subject (2.6%) experiencing a Grade 5 TEAE.

The most frequently reported TEAEs by PT (those occurring in ≥ 25% of subjects) were febrile neutropenia, maculopapular rash and electrocardiogram QT prolonged. Frequency of TEAEs related to myelosuppression, such as anaemia, were seen more often at both doses in the chemotherapy pre-treated paediatrics than in treatment naïve adult patients. The most common TEAE was febrile neutropenia. Cardiac TEAEs (QT prolongation, sinus tachycardia, ejection fraction decreased) and rash occurred more often at the higher dose.

For related TEAEs in study 1421, febrile neutropenia was observed at comparable frequency (44.7% vs. 48.3%) whereas rash was more frequent than in adults (42.1% vs. 32.3%).

Serious TEAEs (SAEs) occurred in 21/38 subjects (55.3%). The majority of SAEs were reported in the SOCs Blood and Lymphatic System Disorders and Infections and Infestations (11/38 subjects, 28.9% in each class). The most commonly reported SAE was febrile neutropenia (11/38 subjects, 28.9%). Rash maculopapular was reported in 6 subjects (15,8%) and pyrexia in 2 subjects (5.3%).

Treatment-related SAEs occurred in 20/38 subjects (52.6%). The majority of treatment-related SAEs were reported in the SOCs Blood and Lymphatic System Disorders (11/38 subjects, 28.9%) and Infections and Infestations (9/38 subjects, 23.7%). The most commonly reported treatment-related SAEs by PT were febrile neutropenia (11/38 subjects, 28.9%), rash maculopapular (6/38 subjects, 15.8%) and colitis (2/38 subjects, 5.3%).

Within serious and serious related TEAEs, febrile neutropenia occurred at a significantly higher rate in both paediatric studies than in the adult studies: in study 1421, frequency was 28.9%, all were considered related, whereas in the pooled adult population, frequency was 10.1%, considering induction only 5.3%.

LVEF appeared to decrease slightly from BL. Nearly 25% of patients (8 of 35) experienced reduced LVEF ≤ 50% during the study. 1 SAE of decreased injection fraction (36%, grade 3) was reported as DLT during cycle 1.

No deaths occurred while subjects received protocol therapy in either study. A total of 12 deaths occurred during the protocol-defined Follow-up Phase (i.e., after subjects had completed the Treatment Phase of the study); none of these were considered related to protocol therapy.

2.5. Uncertainties and limitations about unfavourable effects

- Acknowledging the orphan status of AML, the numbers of paediatric patients are small and derive mainly from a sole, single arm, open label study, with 38 paediatric patients (from 1 to 21 years of age) with relapsed AML (phase 1/2 study AAML1421). Consequently, numbers in the different paediatric age strata are also small.
- No paediatric safety data have been presented, analysed or discussed according to the age strata.
- Long-term safety data derives from this single study: only preliminary data has been provided for the events of death and cardiovascular safety. According to the MAH further data is not available.
- Long-term data on subsequent treatments are not available. These data are prerequisite for the interpretation of long-term safety.
- Considering cumulative exposure to anthracyclines, studies excluded patients above certain pre-dose thresholds, but due to missing data it is unclear whether current recommendations for upper limits, i.e. higher than the Vyxeos-SmPC-recommended maximal cumulative anthracycline dose, were followed.

2.6. Effects Table

Table 8.6.1. Study AAML1421: Effects Table for Vyxeos liposomal in paediatric and young adult patients from 1 year of age to 21 years of age in the treatment of relapsed AML (data cut-off: 30.6.2019)

Effect	Short description	Unit	Result	Uncertainties / Strength of evidence	References (Clinical study report)
ORR (CR + CRp) Primary efficacy endoint	After CPX-351 (Cycle 1) followed by FLAG (Cycle 2)	%	68%	very limited data of previous therapies including HSCT, no data with regard the use of HSCT as consolidation in patients achieving CR, no long-term efficacy data	Study AAML1421
Unfavourable Effects					
Number of patients, all		N	38	Safety Analysis set	Study AAML1421
Any related TEAE	Number of patients	(n)%	30 (78.9)	Single arm, open label study, with small numbers, limited/pending long term data.	Study AAML1421
Any Grade 3 TEAEs	Number of patients	(n)%	29 (76.3)		Study AAML1421
Any Grade 4 TEAEs	Number of patients	(n)%	4 (10.5)		Study AAML1421
Any Grade 5 TEAEs	Number of patients	(n)%	1 (2.6)		Study AAML1421
Any SAE - febrile neutropenia -maculopapular rash -pyrexia	Number of patients	(n)%	21 (55.3) 11 (28.9) 6 (15.8) 2 (5.3)		Study AAML1421
Any Related SAE	Number of patients		30 (52.6)		Study AAML1421

Abbreviations: PP, per protocol. AE, adverse event; SAE, serious adverse event; TEAE, treatment emergent adverse event; Notes:

2.7. Benefit-risk assessment and discussion

2.7.1. Importance of favourable and unfavourable effects

Vyxeos liposomal has demonstrated that majority of study population (study AAML1421) with relapsed AML achieved substantial response and ended up with CR. This is important given the extremely poor prognosis of these patients and their unmet medical need. Secondary endpoint supports the primary outcome.

There is no direct clinical relevance of CR in AML treatment. Its clinical relevance is based on the fact, that CR/CRp/CRi is normally aimed for as the basis for HSCT after (re-)induction therapy, being the only therapeutic option with curative intent in a high-risk AML setting as RR AML. However, while it is acknowledged that targeting CR2 is of utmost importance, the long-term outcome and contextualisation of the observed efficacy results is difficult. This is due limited data available regarding the use of HSCT as consolidation in patients achieving response (CR2). Importantly, chemotherapy on its own is not likely to have major long-term benefit in patients with relapsed AML.

Since the MAH is no longer pursuing the indication for paediatric patients with R/R AML, it has not provided the requested data to assess the clinical relevance of the efficacy results nor provided the requested long-term efficacy data. Thus, while this data would be of interest, these issues are not pursued further.

The pivotal study (study AAML1421) included also patients 18-21 years. This issue somewhat complicates the assessment of the efficacy because for these "young adult" patients there are possible therapeutic options, like gilteritinib, available. Efficacy results have not been presented by age category, and therefore B/R cannot currently be assessed. PopPK analyses suggested that exposures increased significantly in young adults 18-21 years. Based on current PK data, the proposed dose is questionable for young adults aged 18-21 years. However, since the MAH is no longer pursuing the indication for paediatric patients with R/R AML the acceptability of the proposed indication (wording, patient population, posology) is not relevant anymore.

Considering the limitations of the current paediatric data, deriving mainly from a small, single arm study, with limited long-term data and the lack of adequate safety data in adult RR-AML patients, the interpretation and contextualisation of the submitted paediatric safety data is somewhat restricted. However, the adequacy and sufficiency of the totality of the submitted data for the assessment of the overall safety of Vyxeos liposomal in the treatment of paediatric patients with RR-AML is considered acceptable, in the current setting of a PI texts variation, to inform the prescriber, as per guidance, of the availability of the such data.

2.7.2. Balance of benefits and risks

Benefit-risk balance of Vyxeos liposomal in paediatric and young adult patients from 1 year of age to 21 years of age in the treatment of relapsed or refractory AML is negative but remains positive for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

2.7.3. Additional considerations on the benefit-risk balance

The MAH has withdrawn the application for the 1-year additional data marketing exclusivity.

2.8. Conclusions

The overall B/R of Vyxeos liposomal remains positive for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC to include relevant information in paediatric patients based on results from the paediatric clinical study AAML1421. The Package leaflet is updated accordingly.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-001858-PIP02-16-M03 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Vyxeos Liposomal-H-C-0004282-II-0018'