NDA 209401
IND 072939

WRITTEN REQUEST – AMENDMENT 1

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Michael J. Taptykoff
Manager, Regulatory Affairs
2005 Market Street, Suite #2100
Philadelphia, PA 19103

Dear Mr. Taptykoff:[1]

Please refer to your correspondence dated April 10, 2023, requesting changes to FDA's August 28, 2020, Written Request for pediatric studies for Vyxeos (daunorubicin and cytarabine).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on August 28, 2020, remain the same. (Text added is underlined. Text deleted is strikethrough.)

These studies investigate the potential use of (daunorubicin and cytarabine) liposome for injection in the treatment of acute myeloid leukemia in pediatric patients 1 to <17 years old.

BACKGROUND:

AML is a life-threatening cancer and represents a condition with high unmet medical need. It is the second most common form of leukemia in children. In the United States, approximately 700 patients per year under the age of 20 are diagnosed with AML. For children and adolescents with AML, 5-year survival rates are estimated to be between 60 to 75%. Additionally, up to 10% of children who are diagnosed with AML will be refractory to induction chemotherapy, and AML will recur in up to 40% of initial responders. AML which is primary refractory or relapsed continues to carry a poor prognosis characterized by low response rates to salvage chemotherapy regimens, short response durations, and poor survival.

(Daunorubicin and cytarabine) liposome for injection is approved for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). (Daunorubicin and cytarabine)

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liposome received orphan drug designation on August 22, 2008; therefore, studies to be conducted under the Pediatric Research Equity Act (PREA) do not apply.

The response of AML to cytotoxic therapies, including (daunorubicin and cytarabine) liposome, is expected to be sufficiently similar between adults and pediatric patients to allow extrapolation of efficacy in patients with t-AML or AML-MRC. However, no data are available on the systemic exposure of (daunorubicin and cytarabine) liposome at the approved adult dose. Therefore, studies are needed to determine a safe and appropriate pediatric dose of (daunorubicin and cytarabine) liposome. Additionally, there are no data in adults on the efficacy of (daunorubicin and cytarabine) liposome for the treatment of de novo AML. Therefore, a pediatric study is needed to determine the efficacy of (daunorubicin and cytarabine) liposome as a component of a multidrug regimen for de novo AML. Studies in neonates and infants less than 1 year are requested in the newly-diagnosed de novo AML setting.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on (daunorubicin and cytarabine) liposome for injection, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on the review of the available nonclinical information, no additional nonclinical studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

  Study 1: AAML1421 – COG multicenter Phase 1/2, single-arm study of (daunorubicin and cytarabine) liposome alone followed by fludarabine, cytarabine, and G-CSF (FLAG) for children with AML in first relapse

  Study 2: CPX-MA-1201 – Single-arm study of (daunorubicin and cytarabine) liposome for injection monotherapy for children with relapsed leukemia or lymphoma.

Study 3: AAML1831 – COG multicenter Phase 3 randomized trial for patients with de novo AML comparing standard therapy including gemtuzumab ozogamicin (GO) to (daunorubicin and cytarabine) liposome with GO [and the addition of the FLT3 inhibitor gilteritinib for patients with FLT3 mutations] – Arms A and B only (GO + standard therapy vs GO + (daunorubicin and cytarabine) liposome)

- *Study Objectives:*

Study 1: AAML1421

- Primary objectives:
  - Determine a recommended phase 2 dose (RP2D) and the toxicities associated with (daunorubicin and cytarabine) liposome in pediatric and young adult subjects with RR-AML
  - Estimate the response rate (CR) after (daunorubicin and cytarabine) liposome (Cycle 1) followed by FLAG (Cycle 2) in children with AML in first relapse during the Efficacy Phase.
- Secondary objectives: Describe the PK of plasma (daunorubicin and cytarabine) liposome after (daunorubicin and cytarabine) liposome administration to pediatric and young adult subjects with RR-AML.

Study 2: CPX-MA-1201

- Primary objectives:
  - Determine a safe and tolerable dose of (daunorubicin and cytarabine) liposome in children and adolescents with relapsed or refractory hematologic malignancies and to recommend a dose for future studies;
  - Describe the toxicity and tolerability of (daunorubicin and cytarabine) liposome in children and young adults with hematologic malignancies;
  - Recommend a dose of (daunorubicin and cytarabine) liposome for future studies in young subjects with previously untreated AML; and
  - Describe the PK of plasma (daunorubicin and cytarabine) liposome after (daunorubicin and cytarabine) liposome administration to young subjects with recurrent or refractory hematologic malignancies.
- Secondary objectives: Describe the response in biomarkers of cardiac injury to a single course of (daunorubicin and cytarabine) liposome.

Study 3: AAML1831

- Primary objective: Compare EFS (event-free survival) in children with de novo AML without FLT3 mutations who are randomly assigned to standard induction therapy on Arm A (DA-GO) with daunorubicin, cytarabine (DA) and GO versus Arm B with (daunorubicin and cytarabine) liposome and GO.
- Key secondary objective: compare OS (overall survival) and rates of end of Induction 1 (EOI1) minimal residual disease (MRD) in children with de novo AML without FLT3 mutations who are randomly assigned to standard

induction therapy (Arm A) with DA-GO versus (daunorubicin and cytarabine) liposome and GO (Arm B).

- *Patients to be Studied:*

Study 1: AAML1421
- Patients in first relapse or who were refractory not having received more than 1 induction therapy (dose-finding) and subjects in first relapse (efficacy phase) ages ≥ 1 year to ≤ 21 years.
- 38 subjects total: 6 subjects in the Dose-finding Phase, and 32 subjects in the Efficacy Phase
- A minimum of 25 patients will be < 17 years of age

Study 2: CPX-MA-1201
- Patients with relapsed/refractory hematologic malignancies
    - Dose exploration – ages ≥ 12 months to ≤ 21 years
    - Expansion phase – ≥ 12 months to ≤ 30 years
- 27 subjects total: 9 subjects in the Dose Exploration Phase and 18 subjects in the Expansion Phase
- A minimum of 20 patients will be < 17 years of age

Study 3: AAML1831
- Patients with de novo AML without FLT3 mutations (Arms A and B) less than 22 years old
- It is expected that, consistent with prior enrollment patterns in COG sponsored trials, approximately 75% of patients enrolled in AAML1831 will be < 17 years of age.
- Primary analysis will be performed for Arm A and Arm B which will enroll 1140 subjects (570 subjects in each arm).

- *Study endpoints:*

Study 1: AAML1421
- *Pharmacokinetic/pharmacodynamic endpoints:*
    - maximum plasma concentration (C_{max})
    - time to C_{max} (T_{max})
    - terminal half-life ($t_{1/2}$)
    - area under the plasma concentration-time curve for the dosing interval (AUC_{tau})
    - clearance (CL)
    - volume of distribution at steady state (V_{ss})

- *Primary endpoint(s):*
    - Dose-finding – Recommended Phase 2 dose

- Efficacy Phase – CR after up to 2 cycles

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include adverse events (AEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), deaths, laboratory tests, vital signs, measures of cardiac function

Study 2: CPX-MA-1201

- *Pharmacokinetic/Pharmacodynamic endpoints:* Cmax, Tmax, t1/2, AUCtau, CL, and Vss.

- *Primary endpoint(s):* Recommended Phase 2 dose

- *Key secondary endpoints:* CR after 1 course of (daunorubicin and cytarabine) liposome

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include known biologic safety concerns and monitoring, including serum copper levels
  - Safety outcomes must also include AEs, SAEs, DLTs, deaths, laboratory tests, vital signs, physical exams, ECGs, and cardiotoxicity biomarkers

Study 3: AAML1831

- *Pharmacokinetic/Pharmacodynamic endpoints: none*

- *Primary efficacy endpoint(s):* EFS (defined as time from randomization to earliest of induction failure, relapse, or death from any cause)

- *Key secondary efficacy endpoint:* OS

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include known biologic safety concerns and monitoring.
  - Important identified risks are:
    - Cardiotoxicity
    - Serious or fatal hemorrhage
    - Copper overload
  - Important potential risks are:
    - Hypersensitivity reactions
    - Tissue necrosis
    - ~~Embryo fetal toxicity~~

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1: AAML1421

Dose-finding Phase: modified rolling 6 trial design – 2-6 patients enrolled per dose level

Efficacy Phase: single arm Simon 2-stage design

- Null hypothesis: overall response rate (CR + CRp) after up to 2 cycles of therapy ≤ 40%
- Alternative hypothesis: overall response rate was ≥ 60%
- Stage 1 – 12 patients; if ≥ 6 responses then enroll Stage 2
- Stage 2 – 26 additional patients

Safety Analyses: descriptive statistics will be used to summarize safety endpoints

Pharmacokinetic Analyses:

- Individual plasma concentrations listed by subject and summarized by study cohort, day and nominal time point using descriptive statistics.
- Pharmacokinetic concentrations summarized for the PK Analysis Set, including subjects with both intensive and sparse sampling schemes.
- Individual plasma PK parameters listed by subject and summarized for each study cohort using descriptive statistics.

Study 2: CPX-MA-1201

Dose Exploration – modified rolling 6 trial design – minimum of 2 evaluable patients per dose level

Dose Expansion – 12 additional

Safety Analyses: descriptive statistics will be used to summarize safety endpoints

Pharmacokinetic Analyses:

- Individual plasma concentrations listed by subject and summarized by study cohort, day and nominal time point using descriptive statistics.
- Pharmacokinetic concentrations summarized for the PK Analysis Set, including subjects with both intensive and sparse sampling schemes.
- Individual plasma PK parameters listed by subject and summarized for each study cohort using descriptive statistics.

Study 3: AAML1831

The primary objective for AAML1831 is to compare the EFS in patients without FLT3 mutations receiving (daunorubicin and cytarabine) liposome + GO to those receiving DA + GO (analysis includes only Arms A and B). With approximately 534 patients without FLT3 mutations on Arm A and Arm B each, this study will have at least 80% power using 2-sided log-

rank test with 0.05 type I error to detect an EFS hazard ratio of 0.762 which corresponds to an 8.4% difference in 5-year EFS (54.8% vs 63.2%).

The key secondary endpoint of OS will be evaluated in the ITT population only if a significant difference is found on EFS analysis.

The statistical analysis plan (SAP) will be submitted for review by and agreement with the Agency.

Safety Analyses: All safety data will be summarized and listed by treatment arm.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - Dosage form: Sterile, preservative-free, purple, lyophilized cake for reconstitution supplied in a clear glass 50 mL single-use vial for injection. Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine.

  - Route of administration: intravenous

  - Regimen(s):

    - **Study 1 AAML1421:**
      - Cycle 1: 2 doses of IT cytarabine (with age-based dosing) along with (daunorubicin and cytarabine) liposome administered IV over 90 minutes on Days 1, 3, and 5.
        - (Daunorubicin and cytarabine) liposome starting dose level: (daunorubicin 59.4 mg/m^2 and cytarabine 135 mg/m^2) liposome Days 1, 3 and 5.
        - Efficacy phase – patients will be treated at the RP2D
      - Cycle 2: FLAG.

- **Study 2 CPX-MA-1201:**
  - Single course of (daunorubicin and cytarabine) liposome IV Days 1, 3, and 5
  - Dose levels of (daunorubicin and cytarabine) liposome: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1, 3 and 5 (dose level 1), (daunorubicin 59.4 mg/m^2 and cytarabine 135 mg/m^2) liposome IV on Days 1, 3 and 5 (dose level 2).
  - MTD: All subjects in the Expansion Phase will receive a single course of (daunorubicin and cytarabine) liposome at the MTD.
  - Intrathecal cytarabine at the investigator's discretion in subjects with microscopic disease in cerebrospinal fluid and in those at high risk for central nervous system failure.

- **Study 3 AAML1831:**
  - Randomized to treatment with daunorubicin + cytarabine (DA) + GO (Arm A) or treatment with (daunorubicin and cytarabine) liposome + GO (Arm B).
    - (Daunorubicin and cytarabine) liposome: (daunorubicin 60 mg/m^2 and cytarabine 136.4 mg/m^2) liposome IV on Days 1, 3 and 5 of Induction 1 and (daunorubicin 50 mg/m^2 and cytarabine 113.6 mg/m^2) liposome IV on Days 1, 3, and 5 of Induction 2.

  Results of cytogenetics, molecular diagnostics, transcriptome sequencing, and end induction multidimensional flow cytometry will be used to risk stratify patients into HR and LR groups.

  - Arm A and B Low Risk Group 1 (LR1): 4 total courses of chemotherapy, including the 2 courses described above for Inductions 1 and 2, along with Intensification 1 (cytarabine / etoposide) and Intensification 2 (high dose cytarabine / asparaginase [Capizzi II]).

  - Arm A and B Low Risk Group 2 (LR2): 5 total courses of chemotherapy, including the 2 courses described above for Inductions 1 and 2, along with Intensification 1 (cytarabine / etoposide), Intensification 2 (mitoxantrone / cytarabine [MA]), and Intensification 3 (Capizzi II).

  - Arm A and B High Risk Group (HR): 3 courses of chemotherapy (Inductions 1 and 2 along with Intensification 1 [cytarabine / etoposide]) and then proceed to HSCT if a suitable donor can be identified. Patients without suitable donors will receive 5 courses of chemotherapy per their primary randomization.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that (daunorubicin and cytarabine) liposome for injection is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation.

  In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[2] You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[3] and referenced in the guidance for industry *Providing Regulatory Submissions in*

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[3] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before ~~March 1, 2026~~ June 30, 2029. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated August 28, 2020, and as amended by this letter must be submitted to the Agency on or before June 30, 2029, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION**

REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[4]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Suria Yesman, Senior Regulatory Project Manager, at Suria.Yesmin@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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Attention: Michael J. Taptykoff
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Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on (daunorubicin and cytarabine) liposome for injection, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

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  Based on the review of the available nonclinical information, no additional nonclinical studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

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  Study 2: CPX-MA-1201 – Single-arm study of (daunorubicin and cytarabine) liposome for injection monotherapy for children with relapsed leukemia or lymphoma.

Study 3: AAML1831 – COG multicenter Phase 3 randomized trial for patients with de novo AML comparing standard therapy including gemtuzumab ozogamicin (GO) to (daunorubicin and cytarabine) liposome with GO [and the addition of the FLT3 inhibitor gilteritinib for patients with FLT3 mutations] – Arms A and B only (GO + standard therapy vs GO + (daunorubicin and cytarabine) liposome)

- *Study Objectives:*

Study 1: AAML1421

- Primary objectives:
  - Determine a recommended phase 2 dose (RP2D) and the toxicities associated with (daunorubicin and cytarabine) liposome in pediatric and young adult subjects with RR-AML
  - Estimate the response rate (CR) after (daunorubicin and cytarabine) liposome (Cycle 1) followed by FLAG (Cycle 2) in children with AML in first relapse during the Efficacy Phase.
- Secondary objectives: Describe the PK of plasma (daunorubicin and cytarabine) liposome after (daunorubicin and cytarabine) liposome administration to pediatric and young adult subjects with RR-AML.

Study 2: CPX-MA-1201

- Primary objectives:
  - Determine a safe and tolerable dose of (daunorubicin and cytarabine) liposome in children and adolescents with relapsed or refractory hematologic malignancies and to recommend a dose for future studies;
  - Describe the toxicity and tolerability of (daunorubicin and cytarabine) liposome in children and young adults with hematologic malignancies;
  - Recommend a dose of (daunorubicin and cytarabine) liposome for future studies in young subjects with previously untreated AML; and
  - Describe the PK of plasma (daunorubicin and cytarabine) liposome after (daunorubicin and cytarabine) liposome administration to young subjects with recurrent or refractory hematologic malignancies.
- Secondary objectives: Describe the response in biomarkers of cardiac injury to a single course of (daunorubicin and cytarabine) liposome.

Study 3: AAML1831

- Primary objective: Compare EFS (event-free survival) in children with de novo AML without FLT3 mutations who are randomly assigned to standard induction therapy on Arm A (DA-GO) with daunorubicin, cytarabine (DA) and GO versus Arm B with (daunorubicin and cytarabine) liposome and GO.
- Key secondary objective: compare OS (overall survival) and rates of end of Induction 1 (EOI1) minimal residual disease (MRD) in children with de novo AML without FLT3 mutations who are randomly assigned to standard

induction therapy (Arm A) with DA-GO versus (daunorubicin and cytarabine) liposome and GO (Arm B).

- *Patients to be Studied:*

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- Patients in first relapse or who were refractory not having received more than 1 induction therapy (dose-finding) and subjects in first relapse (efficacy phase) ages ≥ 1 year to ≤ 21 years.
- 38 subjects total: 6 subjects in the Dose-finding Phase, and 32 subjects in the Efficacy Phase
- A minimum of 25 patients will be < 17 years of age

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- Patients with relapsed/refractory hematologic malignancies
    - Dose exploration – ages ≥ 12 months to ≤ 21 years
    - Expansion phase – ≥ 12 months to ≤ 30 years
- 27 subjects total: 9 subjects in the Dose Exploration Phase and 18 subjects in the Expansion Phase
- A minimum of 20 patients will be < 17 years of age

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- Patients with de novo AML without FLT3 mutations (Arms A and B) less than 22 years old
- It is expected that, consistent with prior enrollment patterns in COG sponsored trials, approximately 75% of patients enrolled in AAML1831 will be < 17 years of age.
- Primary analysis will be performed for Arm A and Arm B which will enroll 1140 subjects (570 subjects in each arm).

- *Study endpoints:*

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- *Pharmacokinetic/pharmacodynamic endpoints:*
    - maximum plasma concentration (C_{max})
    - time to C_{max} (T_{max})
    - terminal half-life ($t_{1/2}$)
    - area under the plasma concentration-time curve for the dosing interval (AUC_{tau})
    - clearance (CL)
    - volume of distribution at steady state (V_{ss})

- *Primary endpoint(s):*
    - Dose-finding – Recommended Phase 2 dose

- Efficacy Phase – CR after up to 2 cycles

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include adverse events (AEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), deaths, laboratory tests, vital signs, measures of cardiac function

Study 2: CPX-MA-1201

- *Pharmacokinetic/Pharmacodynamic endpoints:* Cmax, Tmax, t1/2, AUCtau, CL, and Vss.

- *Primary endpoint(s):* Recommended Phase 2 dose

- *Key secondary endpoints:* CR after 1 course of (daunorubicin and cytarabine) liposome

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include known biologic safety concerns and monitoring, including serum copper levels
  - Safety outcomes must also include AEs, SAEs, DLTs, deaths, laboratory tests, vital signs, physical exams, ECGs, and cardiotoxicity biomarkers

Study 3: AAML1831

- *Pharmacokinetic/Pharmacodynamic endpoints: none*

- *Primary efficacy endpoint(s):* EFS (defined as time from randomization to earliest of induction failure, relapse, or death from any cause)

- *Key secondary efficacy endpoint:* OS

- *Safety Endpoints/Monitoring:*
  - Safety outcomes must include known biologic safety concerns and monitoring.
  - Important identified risks are:
    - Cardiotoxicity
    - Serious or fatal hemorrhage
    - Copper overload
  - Important potential risks are:
    - Hypersensitivity reactions
    - Tissue necrosis

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1: AAML1421

Dose-finding Phase: modified rolling 6 trial design – 2-6 patients enrolled per dose level

Efficacy Phase: single arm Simon 2-stage design

- Null hypothesis: overall response rate (CR + CRp) after up to 2 cycles of therapy ≤ 40%
- Alternative hypothesis: overall response rate was ≥ 60%
- Stage 1 – 12 patients; if ≥ 6 responses then enroll Stage 2
- Stage 2 – 26 additional patients

Safety Analyses: descriptive statistics will be used to summarize safety endpoints

Pharmacokinetic Analyses:

- Individual plasma concentrations listed by subject and summarized by study cohort, day and nominal time point using descriptive statistics.
- Pharmacokinetic concentrations summarized for the PK Analysis Set, including subjects with both intensive and sparse sampling schemes.
- Individual plasma PK parameters listed by subject and summarized for each study cohort using descriptive statistics.

Study 2: CPX-MA-1201

Dose Exploration – modified rolling 6 trial design – minimum of 2 evaluable patients per dose level

Dose Expansion – 12 additional

Safety Analyses: descriptive statistics will be used to summarize safety endpoints

Pharmacokinetic Analyses:

- Individual plasma concentrations listed by subject and summarized by study cohort, day and nominal time point using descriptive statistics.
- Pharmacokinetic concentrations summarized for the PK Analysis Set, including subjects with both intensive and sparse sampling schemes.
- Individual plasma PK parameters listed by subject and summarized for each study cohort using descriptive statistics.

Study 3: AAML1831

The primary objective for AAML1831 is to compare the EFS in patients without FLT3 mutations receiving (daunorubicin and cytarabine) liposome + GO to those receiving DA + GO (analysis includes only Arms A and B). With approximately 534 patients without FLT3 mutations on Arm A and Arm B each, this study will have at least 80% power using 2-sided log-

rank test with 0.05 type I error to detect an EFS hazard ratio of 0.762 which corresponds to an 8.4% difference in 5-year EFS (54.8% vs 63.2%).

The key secondary endpoint of OS will be evaluated in the ITT population only if a significant difference is found on EFS analysis.

The statistical analysis plan (SAP) will be submitted for review by and agreement with the Agency.

Safety Analyses: All safety data will be summarized and listed by treatment arm.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - Dosage form: Sterile, preservative-free, purple, lyophilized cake for reconstitution supplied in a clear glass 50 mL single-use vial for injection. Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine.

  - Route of administration: intravenous

  - Regimen(s):

    - **Study 1 AAML1421:**
      - Cycle 1: 2 doses of IT cytarabine (with age-based dosing) along with (daunorubicin and cytarabine) liposome administered IV over 90 minutes on Days 1, 3, and 5.
        - (Daunorubicin and cytarabine) liposome starting dose level: (daunorubicin 59.4 mg/m^2 and cytarabine 135 mg/m^2) liposome Days 1, 3 and 5.
        - Efficacy phase – patients will be treated at the RP2D
      - Cycle 2: FLAG.

- **Study 2 CPX-MA-1201:**
  - Single course of (daunorubicin and cytarabine) liposome IV Days 1, 3, and 5
  - Dose levels of (daunorubicin and cytarabine) liposome: (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome IV on Days 1, 3 and 5 (dose level 1), (daunorubicin 59.4 mg/m^2 and cytarabine 135 mg/m^2) liposome IV on Days 1, 3 and 5 (dose level 2).
  - MTD: All subjects in the Expansion Phase will receive a single course of (daunorubicin and cytarabine) liposome at the MTD.
  - Intrathecal cytarabine at the investigator's discretion in subjects with microscopic disease in cerebrospinal fluid and in those at high risk for central nervous system failure.

- **Study 3 AAML1831:**
  - Randomized to treatment with daunorubicin + cytarabine (DA) + GO (Arm A) or treatment with (daunorubicin and cytarabine) liposome + GO (Arm B).
    - (Daunorubicin and cytarabine) liposome: (daunorubicin 60 mg/m^2 and cytarabine 136.4 mg/m^2) liposome IV on Days 1, 3 and 5 of Induction 1 and (daunorubicin 50 mg/m^2 and cytarabine 113.6 mg/m^2) liposome IV on Days 1, 3, and 5 of Induction 2.

  Results of cytogenetics, molecular diagnostics, transcriptome sequencing, and end induction multidimensional flow cytometry will be used to risk stratify patients into HR and LR groups.

  - Arm A and B Low Risk Group 1 (LR1): 4 total courses of chemotherapy, including the 2 courses described above for Inductions 1 and 2, along with Intensification 1 (cytarabine / etoposide) and Intensification 2 (high dose cytarabine / asparaginase [Capizzi II]).

  - Arm A and B Low Risk Group 2 (LR2): 5 total courses of chemotherapy, including the 2 courses described above for Inductions 1 and 2, along with Intensification 1 (cytarabine / etoposide), Intensification 2 (mitoxantrone / cytarabine [MA]), and Intensification 3 (Capizzi II).

  - Arm A and B High Risk Group (HR): 3 courses of chemotherapy (Inductions 1 and 2 along with Intensification 1 [cytarabine / etoposide]) and then proceed to HSCT if a suitable donor can be identified. Patients without suitable donors will receive 5 courses of chemotherapy per their primary randomization.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that (daunorubicin and cytarabine) liposome for injection is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation.

  In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[2] You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[3] and referenced in the guidance for industry *Providing Regulatory Submissions in*

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[3] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before June 30, 2029. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated August 28, 2020, and as amended by this letter must be submitted to the Agency on or before June 30, 2029, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION**

REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[4]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Suria Yesman, Senior Regulatory Project Manager, at Suria.Yesmin@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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/s/

MARTHA B DONOGHUE
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