CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209401Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209401	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Vyxeos Established/Proper Name: CPX-351 (cytarabine and daunorubicin) Dosage Form: liposome for injection Strengths: 100 mg cytarabine and 44 mg daunorubicin		
Applicant: Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)		
Date of Receipt: March 31, 2017		
PDUFA Goal Date: September 30, 2017	Action Goal Date (if different): August 3, 2017	
RPM: Wanda Nguyen, PharmD		
Proposed Indication(s): Treatment of adults with [redacted] (b) (4) therapy related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

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INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	*Nonclinical primary pharmacology, Nonclinical toxicology; genotoxicity, carcinogenicity, and developmental and reproductive toxicity*
NDA 050704 DaunoXome	*FDA's previous finding of safety and effectiveness (nonclinical)*
NDA 021041 DepoCyt	*FDA's previous finding of safety and effectiveness (nonclinical)*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The bridging of the proposed drug product to the two listed drugs has been assessed on the basis of 21 CFR 320.24(b)(6). This 505(b)(2) NDA for VYXEOS® (daunorubicin and cytarabine) Liposome for Injection relies on FDA's prior findings of clinical pharmacology (i.e., metabolism and excretion pathways and drug-drug interactions with cardiotoxic agents and hepatotoxic agents) and nonclinical pharmacology/toxicology (i.e., mechanisms of action, genotoxicity, carcinogenicity, reproductive, and developmental toxicity) for the listed drugs, DepoCyt Injection, and DaunoXome Injection. The Applicant's reliance on FDA's previous findings of safety (PK and nonclinical pharmacology) is justified for the following reasons: (1) The proposed liposomal product and the listed drugs contain the same active pharmaceutical ingredients (cytarabine and daunorubicin). Metabolism, excretion, plasma-protein binding, interactions with drug efflux transporters, metabolizing enzymes, and drug receptors in target/non-target organs are the same for the proposed and listed drug products. (2) The findings of the animal pharmacology, PK, and single- and repeat dose toxicity studies conducted by the Applicant further corroborated the reliance of the NDA on the nonclinical pharmacology findings for the listed drugs. For further details on the nonclinical pharmacology and toxicology data relied upon for the drug product, refer to table 2 in the Reviewer's Guide (\\cdsesub1\evsprod\nda209401\0001\m1\us\12-cov-let\rev-guide.pdf).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
DepoCyt (cytarabine liposome injection)	021041	Y
DaunoXome (daunorubicin citrate liposome injection)	050704	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

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Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form and new combination.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

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*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all*

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of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): DepoCyt

No patents listed ☒ *proceed to question #14*

Listed drug/Patent number(s): DaunoXome

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):
Daunoxome (NDA 50704) – no unexpired patents listed in OB
Depocyt (NDA 21041) – no unexpired patents listed in OB

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

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infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

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Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WANDA D NGUYEN
08/03/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 2, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209401
Product Name and Strength:	Vyxeos (DAUNOorubicin and cytarabine) Liposome for Injection 44 mg DAUNOrubicin and 100 mg cytarabine
Applicant/Sponsor Name:	Celator Pharmaceuticals, Inc. (Jazz Pharmaceuticals Company)
Submission Date:	July 27, 2017 and July 31, 2017
OSE RCM #:	2017-664-2 and 2017-748-2
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Vyxeos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Of note, the carton labeling and container label included a warning to not "(b) (4) Vyxeos with other drugs containing DAUNOrubicin and cytarabine while the Prescribing Information (PI) submitted on July 21, 2017 included a warning to not "interchange" Vyxeos with other drugs containing DAUNOrubicin and cytarabine. DMEPA suggested that the language be consistent between the carton labeling, container label, and PI and therefore recommended to use the statement "(b) (4)" on all labels/labeling. Our current thinking is that the term "(b) (4) without reference to interchange term is sufficient to mitigate the risk of inadvertent substitution. The Division determined that the term "interchange" was more appropriate, and thus the carton and container labeling were updated and included as part of the submission on July 31, 2017.

[a] Garrison N. Human Factors Label and Labeling Review for Vyxeos (NDA 209401). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 25. RCM No.: 2017-664-1 and 2017-748-1.

Reference ID: 4133856

2 CONCLUSION

The revised container label and carton labeling for Vyxeos are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JULY 31, 2017

Container label

(b) (4)

Carton labeling

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4133856

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE B GARRISON
08/02/2017

HINA S MEHTA
08/02/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	**209401**
PMR/PMC Set	3255
Product Name:	VYXEOS (CPX-351)
Applicant Name:	Jazz Pharmaceuticals
ODE/Division:	**OHOP/DHP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

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

2. PMR/PMC Schedule Milestones[2, 3]

Preliminary Protocol/ Analysis Plan Submission: November, 2017
Final Protocol/ Analysis Plan Submission: January, 2018
Study Completion: January, 2019
Final Report Submission: July, 2019

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

Reference ID: 4133211

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

Trial CLTR0308-301 demonstrated an OS benefit of 3.6 months in patients with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia related changes (AML-MRC) treated with VYXEOS vs standard daunorubicin and cytarabine therapy (7+3). However, the safety monitoring across the VYXEOS development program was not sufficient to detect infusion related toxicities. No clinical study monitored vital signs more frequently than daily, and this was only done in the phase 1 dose-finding study (CLTR 0305-101); Studies CLTR0308-204, CLTR0308-205 and CLTR0308-301 required vital sign monitoring only on days 14 and 42 of each cycle. Even with the daily monitoring that only the 48 patients on Study 101 had, infusion reactions that occurred during or soon after the infusion could be missed. Infusion-related reactions and/or hypersensitivity, including serious, life-threatening and fatal infusion reactions, have been associated with liposomal products, including liposomal daunorubicin. These reactions are also associated with non-liposomal daunorubicin and cytarabine. VYXEOS is a liposomal formulation of daunorubicin and cytarabine, such that the potential for these reactions is of concern. With the limited monitoring described above, 7% of patients in the VYXEOS arm had hypersensitivity reactions and 1% had infusion-related reactions. Also, presyncope and grade 3 hypotension occurred at a higher incidence on the VYXEOS arm (5% vs none and 6% vs 1%, respectively), and these could be manifestations of infusion-related toxicity. The goal of this PMR is to further characterize the safety of VYXEOS, specifically with regard to the incidence of infusion-related reactions.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

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3. **<u>For FDAAA PMRs and 506B PMCs only</u>**

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☐ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☒ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Reference ID: 4133211

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

Reference ID: 4133211

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

☒ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☒ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☒ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☒ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

Reference ID: 4133211

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*) ☐ Dose-response clinical trial ☐ Dosing trial (e.g., alternative dosing schedule) ☐ Drug interaction or bioavailability clinical trial (clinical only) ☐ Immunogenicity trial (clinical) ☐ Meta-analysis or pooled analysis of previous clinical trials ☐ Pharmacogenetic or pharmacogenomic clinical trial ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial ☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints) ☒ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT* ☐ Safety outcomes trial (SOT)** ☐ Thorough Q-T clinical trial ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

Reference ID: 4133211

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***
   - ☒ The study/clinical trial meets criteria for a PMR or a PMC.
   - ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
   - ☒ The applicant has adequately justified the choice of milestone dates.
   - ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**
   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer question about a drug's efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety)

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

Reference ID: 4133211

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[10] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION B: PMR/PMC Information

1. PMR/PMC Description

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

2. PMR/PMC Schedule Milestones[11, 12]

Final Protocol Submission:	January 2018
Trial Completion:	January 2021
Final Report Submission:	June 2021

[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[11] *Final protocol, study/trial completion,* and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[12] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

Reference ID: 4133211

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[13] or clinical trial[14] in the text box below.

CPX-351 is intended for patients with AML and impaired renal function in clinic. However, cytarabine is primarily excreted in the urine; and a dose reduction by 50% for creatinine >3 mg/dL is recommended per non-liposome daunorubicin labeling. Around 40% increase in exposures of total daunorubicin and cytarabine as well as greater TEAEs Grade 3 to 5, serious TEAEs and TEAEs leading to death were observed in patients with moderate renal impairment taking CPX-351 at the proposed dosage regimen compared to those in patients with normal renal function. In addition, the effect of severe renal impairment on CPX-351 PK, efficacy and safety has not been tested in the trial. Therefore, a PMR is required to evaluate the potential need of an alternative dosing regimen for patients with moderate and severe renal impairment.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☒ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial

[13] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[14] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

Reference ID: 4133211

postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[15] and Sentinel's postmarket ARIA[16] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☒ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[15] FDA Adverse Event Reporting System (FAERS)

[16] Active Risk Identification and Analysis (ARIA)

Reference ID: 4133211

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

Reference ID: 4133211

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☒ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

Reference ID: 4133211

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☒ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

4. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

5. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

Reference ID: 4133211

6. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[17]

4. **The PMR/PMC is clear, feasible, and appropriate[18] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

5. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

6. ☐ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety)

[17] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[18] See POLICY section of CDER MAPP 6010.9.

Reference ID: 4133211

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/s/

BARRY W MILLER
08/01/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 25, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209401
Product Name and Strength:	Vyxeos (daunorubicin and cytarabine) Liposome for Injection 44 mg daunorubicin and 100 mg cytarabine
Applicant/Sponsor Name:	Celator Pharmaceuticals, Inc. (Jazz Pharmaceuticals Company)
Submission Date:	July 13, 2017 and July 19, 2017
OSE RCM #:	2017-664-1 and 2017-748-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Vyxeos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Division has communicated with the Applicant that the daunorubicin component be listed first i.e. daunorubicin and cytarabine liposome. The carton labeling is unacceptable from a medication error perspective. To mitigate the risk of preparation errors we recommend including the statement on the carton labeling, "Carefully swirl the contents of the vial for 5 minutes" in bold font.

[a] Garrison N. Human Factors Label and Labeling Review for Vyxeos (NDA 209401). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 12. RCM No.: 2017-664 and 2017-748.

Reference ID: 4129835

3 RECOMMENDATIONS FOR CELATOR PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling
   1. Include the statement in bold font on the side display panel, "**Carefully swirl the contents of the vial for 5 minutes.**" We recommend this revision to mitigate the risk of preparation errors and to bring prominence to this important information.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4129835

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE B GARRISON
07/25/2017

HINA S MEHTA
07/27/2017

LABEL, LABELING, AND LABEL COMPREHENSION RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 12, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209401
Product Name and Strength:	Vyxeos (daunorubicin and cytarabine) Liposome for Injection 44 mg daunorubicin and 100 mg cytarabine
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celator Pharmaceuticals, Inc. (Jazz Pharmaceuticals Company)
Submission Date:	March 31, 2017, May 15, 2017, June 2, 2017, June 19, 2017 and June 22, 2017
OSE RCM #:	2017-664 and 2017-748
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

Reference ID: 4123293

1 REASON FOR REVIEW

Celator Pharmaceuticals, Inc. is developing Vyxeos (daunorubicin and cytarabine) liposome for injection to be indicated for the treatment of adults with [redacted] (b) (4) under NDA 209401. Thus, the Division of Hematology Products (DHP) requested that DMEPA evaluate the Applicant's proposed Prescribing Information (PI), container label, and carton labeling submitted on March 31, 2017, May 15, 2017, June 2, 2017, June 19, 2017 and June 22, 2017. Additionally, Celator conducted a label comprehension study to evaluate the proposed labeling. We evaluated the results from the label comprehension study to ensure that the intended user population is able to understand the dosing and dosing calculations required to prescribe and prepare the product for administration.

1.1 REGULATORY HISTORY

The protocol for the label comprehension study was submitted to the Agency and comments were provided to Celator Pharmaceuticals on July 26, 2016[a]. We confirmed that our comments were implemented.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other (Labeling Comprehension Studies)	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

[a] Garrison, N. Human Label Comprehension Protocol Review (IND 072939). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jul 21. 15 p. OSE RCM No.: 2016-1034.

Reference ID: 4123293

3.1 LABEL COMPREHENSION STUDY

3.1.1 Methodology:

Celator conducted a label comprehension study to evaluate the ability of oncology healthcare professionals (HCPs) to comprehend the dosing information and dosing calculations required for Vyxeos based on the draft PI, container label, and carton labeling. DMEPA reviewed methodology for the label comprehension study on July 21, 2016[b] and provided recommendations on the order and format of the comprehension questions and the introductory script, which were communicated to the Applicant. We confirmed that the Applicant has addressed all of our comments in the label comprehension study results.

3.1.2 Human factors label comprehension study results

With regard to the results of the label comprehension study, errors occurred in accurately prescribing a dose, accurately preparing a dose, and accurately calculating cumulative daunorubicin exposure (See Appendix F for detailed errors that occurred in the Study).

Errors in accurately prescribing a dose of Vyxeos

Oncologists made errors when prescribing a first induction course, second induction course, and a consolidation course of Vyxeos. The errors occurred because oncologists prescribed the dose based on mL of Vyxeos, on units of Vyxeos, on mass of daunorubicin, on mass of cytarabine, or on the total of both agents instead of the mass of each agent. The Applicant proposes removin (b) (4) in the labels and labeling. Additionally, the review team revised the dose and schedule table for Vyxeos to include both active ingredients in the dose column for each course of Vyxeos. In addition, since Vyxeos is a cytotoxic drug, double checks are often required at the time of dispensing by two pharmacists and prior to administration by two nurses. Our review of the proposed PI determined that the dose of each course of therapy is prominent, and thus no further labeling changes are warranted.

Errors were also seen as participants prescribed the dose of Vyxeos based on a rounded BSA number of 2. The Applicant attributed the rounding based on institutional practice guidelines and not related to the labels and labeling. We acknowledge that institutional practices may vary and have no further labeling recommendations. Also, an error occurred because the BSA from a previous question was used. The Applicant attributed this error to a user interface error from the questionnaire. We acknowledge that the error was not related to the labels and labeling and have no further labeling recommendations.

Error in accurately preparing a dose of Vyxeos

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[b] Garrison, N. Human Label Comprehension Protocol Review (IND 072939). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jul 21. 15 p. OSE RCM No.: 2016-1034.

Reference ID: 4123293

Pharmacists made errors when determining the total number of Vyxeos vials needed to fill an electronic order for a second induction course and a consolidation course of Vyxeos. The errors occurred because pharmacists did not multiply the patient's dose by the BSA, used the incorrect formula, used the correct formula but did the wrong math, or rounded the response down which was considered acceptable. The Applicant proposes to revise Section 2.6 Preparation and Handling Instructions of the PI by including a formula to calculate the volume of reconstituted Vyxeos. Thus, no further labeling changes are warranted.

Error in accurately calculating cumulative daunorubicin exposure

Participants made errors in determining the cumulative daunorubicin exposure in patients with no prior anthracycline exposure and in patients with anthracycline exposure. Some of the errors occurred when participants did not understand the scenario question, did not respond to the question and left it blank, or had an unknown/test error. Our review determined these errors were not related to the labels and labeling of the product, thus no labeling changes are warranted. In addition, errors occurred because participants used the incorrect daunorubicin amount, used the cytarabine mass, used the incorrect formula, or used bad math.

The Applicant has proposed clarifications to the Cumulative Exposure of Daunorubicin per Course of Vyxeos table the PI. The table was revised to remove (b) (4) (b) (4). Additionally, the total amount of daunorubicin per dose and per course for (b) (4) consolidation course was rounded in Table 2 to (b) (4) mg/m^2 and (b) (4) mg/m^2, respectively. The table was relocated to the Warning and Precautions section of the PI since it is part of a risk mitigation strategy pertaining to the cardiotoxicity warning. Instructions were also included in the PI to calculate the prior cumulative anthracycline exposure for patients prior to initiating each cycle of Vyxeos. We acknowledge that oncologists had difficulty completing a simulated electronic order in multiple patients. Oncologists mentioned not having to calculate or manually complete an order for this type of drug due to reliance upon technology and electronic medical record systems. While the study was designed to simulate real-life experiences of oncology healthcare professionals, the use of an online survey was not identical to local and specific systems used by oncology healthcare professionals.

4 LABELS AND LABELING

In addition to the label comprehension study results, we reviewed the proposed PI to determine whether there were any areas that may be vulnerable to confusion that can lead to medication errors. The errors observed in the study can be attributed to incorrect calculations during dose preparation or dose prescribing. The Applicant proposed changes to the Dosage and Administration Section of the PI after the label comprehension study to mitigate errors observed in the study. The labeling changes include removing (b) (4) Instructions were also included to assist pharmacists in calculating the volume of reconstituted product needed to prepare a dose of Vyxeos and for oncology professionals to determine the lifetime cumulative exposure of daunorubicin. The Division of Hematology Products (DHP) proposed relocating the table with cumulative exposure of daunorubicin per course of Vyxeos (cytarabine dose) to the Warnings and Precautions

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section of the PI. In addition, the Applicant is proposing to provide directions for reconstitution on the external carton and include a warning against substitution with other drugs containing cytarabine or daunorubicin on the principal display panel of the label and labeling. We note that during the review of the application, the review team decided to change the order of the established name from "cytarabine and daunorubicin" to "daunorubicin and cytarabine" as a risk mitigation strategy since daunorubicin has a known risk of cardiotoxicity.

Our review of the proposed PI, label, and labeling determined that the preparation and administration information required further revisions to emphasize that this product's dosing is based on the daunorubicin component and should be administered intravenously only. We also recommend revision of the established name to ensure it is consistent with the Office of Generic Drugs list of Tallman letters.

5 CONCLUSION & RECOMMENDATIONS

The results of the label comprehension study demonstrated that additional revisions were needed to the PI, labels and labeling to ensure that the intended user population could comprehend the dosing information and dosing calculations required for Vyxeos prescribing and preparation. In addition, we identified areas within the proposed PI, labels and labeling to increase clarity and prominence of the two active ingredients of Vyxeos. We recognize this application is a priority review to provide needed therapy in an unmet AML population. These changes to the user interface do not require an additional label comprehension study. See Section, 5.1 and 5.2, below, for our recommendations.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information
   1. Section 2.6 Preparation and Handling Instructions
      a. Revise the statement, [redacted] (b) (4) ." to "Calculate the Vyxeos dose based on daunorubicin and individual patient's BSA. Calculate the number of vials of Vyxeos based on the daunorubicin dose." We recommend this revision to emphasize that Vyxeos dosing is based is on the daunorubicin component.
   2. Section 2.7 Administration Instructions
      a. Include the statement, "For intravenous use only." Remove the statement, [redacted] (b) (4) " We recommend this revision to mitigate the risk of administrations errors because cytarabine alone can be administered by intravenous, subcutaneous, and intrathecal route of administration.

5.2 RECOMMENDATIONS FOR CELATOR PHARMACEUTICAL, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container label and Carton labeling

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1. Revise the established name from, “daunorubicin” to “DAUNOrubicin” to ensure consistency with the Office of Generic Drugs list of Tallman letters[c].
2. Reverse of the order of established names to read as “DAUNOrubicin and cytarabine” throughout the container label and carton labeling. The strength expression should also be changed to read as “44 mg/100 mg per vial.”
3. Relocate the route of administration statement, “FOR INTRAVENOUS USE ONLY” right underneath the strength presentation.
4. Bold the statement, “Discard unused portion” on the principal display panel to bring prominence to important handling information.

B. Container label
   1. If space will allow, relocate the reconstitution and dilution statement to the principal display panel.

C. Carton labeling
   1. Include the statement, “Rx only” on the principal display panel as required by Section 503(b)(4)(A) of the Federal Food, Drug and Cosmetic Act.
   2. Include the statement “Must be Reconstituted, then diluted” on the Principal Display Panel (PDP). We recommend this to minimize the risk of administering the product as an intravenous bolus.
   3. Relocate the net quantity statement (i.e. one vial) on the PDP in accordance with 21 CFR 201.51.
   4. Increase the font size of the warning statement, “Do not (b) (4) with other drugs containing cytarabine or DAUNOrubicin” to bring prominence to this important information.

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013, lines [479-492]. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Reference ID: 4123293

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vyxeos that Jazz Pharmaceuticals submitted on March 31, 2017.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Vyxeos</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>Daunorubicin and cytarabine</td></tr>
<tr><td>Indication</td><td>For the treatment of adults with [redacted] (b) (4) [redacted] therapy-related AML (t-AML) or AML with myelodysplasia-related changes</td></tr>
<tr><td>Route of Administration</td><td>Intravenous</td></tr>
<tr><td>Dosage Form</td><td>Liposome for injection</td></tr>
<tr><td>Strength</td><td>Each Vyxeos vial contains 44 mg of daunorubicin [redacted] (b) (4) [redacted] and 100 mg cytarabine</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th rowspan="2">Therapy</th><th colspan="2">Administered intravenously as a 90-minute infusion</th></tr>
<tr><th>Dose</th><th>Dosing Schedule</th></tr>
<tr><td>First Induction Course</td><td>100 mg/44 mg per m^2</td><td>Days 1, 3, and 5</td></tr>
<tr><td>Subsequent Induction [redacted] (b) (4)</td><td>100 mg/44 mg per m^2</td><td>Days 1 and 3</td></tr>
<tr><td>Consolidation [redacted] (b) (4)</td><td>65 mg/29 mg per m^2</td><td>Days 1 and 3</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>As a sterile, preservative-free, purple, lyophilized cake, [redacted] (b) (4) [redacted], in a single- [redacted] (b) (4) vial. Each Vyxeos vial contains 100 mg cytarabine and 44 mg daunorubicin.</td></tr>
<tr><td>Storage</td><td>Store unreconstituted Vyxeos vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect from light.</td></tr>
</table>

Reference ID: 4123293

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 7, 2017, we searched the L:drive and AIMS using the terms, CPX-351 and Vyxeos to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one label comprehension protocol review[d] and one proprietary name review[e]. We confirmed that our previous recommendations were implemented or considered.

[d] Garrison, N. Label Comprehension Protocol Review for CPX-351 (IND 072939). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUL 21. 14p. OSE RCM No.: 2016-1034.

[e] Garrison, N. Proprietary Name Review for Vyxeos (IND 072939). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 15. Panorama No. 2015-47417.

Reference ID: 4123293

APPENDIX F. LABEL COMPREHENSION STUDY

Response to Information Request dated May 15, 2017

Application 209401 - Sequence 0010 - 1.11.3 Clinical Information Amendment –

Response to Information Request dated June 2, 2017

Application 209401 - Sequence 0018 - 0018 (18) 06/02/2017 ORIG-1 /Multiple Categories/Subcategories

Response to Information Request dated June 19, 2017

Application 209401 - Sequence 0028 - 0028 (28) 06/19/2017 ORIG-1 /Multiple Categories/Subcategories

Response to Information Request dated June 22, 2017

Application 209401 - Sequence 0030 - 0030 (30) 06/22/2017 ORIG-1 /Multiple Categories/Subcategories

Reference ID: 4123293

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Vyxeos labels and labeling submitted by Jazz Pharmaceuticals on March 31, 2017, May 15, 2017, June 1, 2017, June 19, 2017 and June 22, 2017.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Container label

(b) (4)

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NICOLE B GARRISON
07/12/2017

HINA S MEHTA
07/12/2017

QUYNHNHU T NGUYEN
07/14/2017

MISHALE P MISTRY
07/17/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 7/14/17

To: Wanda Nguyen, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Katie Davis, Team Leader
OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container labeling) for VYXEOS (daunorubicin and cytarabine) liposome for injection, for intravenous use
NDA 209401

In response to your labeling consult request dated April 6, 2017, we have reviewed the draft Package Insert and Carton/Container labeling for VYXEOS (daunorubicin and cytarabine) liposome for injection, for intravenous use (Vyxeos). This review is based upon the version of the draft PI emailed to OPDP on July 7, 2017 and the Carton/Container labeling emailed to OPDP on July 13, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS **and**	(b) (4)	OPDP notes that the table of adverse reactions in 6.1 (Table 3) and the list of the most common adverse reactions in the Highlights section are not consistent. For example, the terms "hemorrhage," "mucositis," "musculoskeletal pain," "dyspnea," and "arrhythmia" do not appear in Table 3. Additionally, Table 3 includes " (b) (4) at a rate of

Reference ID: 4124873

6.1 Clinical Trials Experience	(b) (4)	(b) (4) %, given the ≥25% cutoff for ARs in the Highlights, "(b) (4) should be included in that section. OPDP also notes that the term "edema" is used in the Highlights section and the term (b) (4) edema" is used in Table 3. OPDP recommends revising to use a consistent term in both sections. We also recommend revising the list of ARs in the Highlights section to appear in a descending order of incidence. We acknowledge that there is a comment to the sponsor to revise the table and to include a descriptive paragraph that includes ARs occurring during the consolidation period and, therefore, that the AR presentation may change. However, as we are unable to review the revised AR presentation at this time our comments are based on the current label.
2.1 Recommended Dosage		As it is currently written, this sentence is confusing (b) (4) We suggest revising to move the phrasing about "unacceptable toxicity" up to the first line regarding initiation of consolidation, similar to the way the sentence about initiating the second induction cycle is written. E.g.: "Administer the first consolidation cycle 5 to 8 weeks after the start of the last induction if there was no unacceptable toxicity with VYXEOS . . . Do not start VYXEOS consolidation until the absolute neutrophil count recovers to greater than 0.5 Gi/L and the platelet count recovers to greater 50 Gi/L."
5.4 Hypersensitivity Reactions		Have any serious or fatal hypersensitivity reactions also been observed with the Vyxeos product? If so, we recommend revising this sentence to also include the proprietary name "Vyxeos" in order to avoid distancing the product from this adverse reaction. E.g., "Serious or fatal hypersensitivity reactions . . . have been reported with daunorubicin, cytarabine, and Vyxeos."
6.1 Clinical Trials Experience		OPDP recommends including the number of patients who experienced each of these adverse reactions as this may provide context for these fatal ARs.

Reference ID: 4124873

	(b) (4)	E.g., "Fatal adverse reactions on the VYXEOS arm included infection (n=X) . . ."
6.1 Clinical Trials Experience		OPDP notes that the list of ARs in this section includes (b) (4) If available, we recommend that the incidence rates be presented for all of the ARs in this section in order to be internally consistent and to be more informative for providers.
14 CLINICAL STUDIES		OPDP notes (b) (4) . OPDP suggests including clinically pertinent exclusion criteria as this is important to qualify the design and conduct of the trial and also to be consistent with the description of clinical trials in other AML labels (e.g., Rydapt's label includes the statement, "Patients with acute promyelocytic leukemia or therapy-related AML were not eligible.")
14 CLINICAL STUDIES	(b) (4)	The criteria by which "adverse karyotype" was determined may be informative for prescribers.
17 PATIENT COUNSELING INFORMATION		Counseling information from section 5.2 should be included in this section.
17 PATIENT COUNSELING INFORMATION	(b) (4)	OPDP notes that this recommendation doesn't include the actual symptoms of heart failure. OPDP suggests including the reportable symptoms of heart failure (e.g., Shortness of breath; fatigue and weakness; edema in legs, ankles and feet; rapid or irregular heartbeat; reduced ability to exercise; persistent cough or wheezing with white or pink blood-tinged phlegm; ascites; sudden weight gain; chest pain) as this is important information for prescribers to share with patients.
17 PATIENT COUNSELING INFORMATION		Consistent with sections 5.7 and 8.3, OPDP recommends revising this section to include contraceptive recommendations for males as well.
17 PATIENT COUNSELING INFORMATION		OPDP recommends including information from section 5.6 regarding the risk of tissue necrosis with extravasation and to add counseling information for patients to immediately report signs or symptoms of extravasation, including a list of these signs and symptoms (e.g., changes in sensation during I.V.

Reference ID: 4124873

		administration such as tingling, burning, discomfort/pain; redness/swelling at the injection site; any blistering, blackening of the skin, or ulceration around the injection site).

Carton/Container Labeling

OPDP does not have any comments on the Carton/Container Labeling at this time.

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4124873

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/s/

RACHAEL E CONKLIN
07/14/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	209401
Brand Name	VYXEOS
Generic Name	CPX-351 (cytarabine:daunorubicin) liposome injection
Sponsor	Celator Pharmaceuticals, Inc.
Indication	Treatment of adults with (b) (4) therapy related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Dosage Form	Liposome injection
Drug Class	Cytarabine is an antineoplastic; Daunorubicin HCI is an antibiotic of the anthracycline group
Therapeutic Dosing Regimen	100 unit/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin base) by 90 minute infusion given on days 1, 3, and 5
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	101 unit/m^2 per day on days 1, 3, and 5
Submission Number and Date	002; 3/31/2017
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 Overall Summary of Findings

Study CLTR0310-206 supports no large mean increases in the ΔQTc interval (i.e., 20 ms) at therapeutic concentrations, based on central tendency analysis (largest 90% CI upper bound was 12.6 ms at 4 h on Day 1) and a lack of concentration-QTc relationship for the components of CPX-351(cytarabine, daunorubicin) and its metabolites. None of the subjects had QTcF >480 ms or ΔQTcF >60 ms.

In this non-randomized, open label Phase 2 study, 26 patients with acute leukemias or myelodysplastic syndrome received CPX-351 at a dose of 100 unit/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin base) administered on study days 1, 3, and 5 by 90 minute infusion. Overall summary of findings is presented in Table 1.

Reference ID: 4112723

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for CPX-351 (FDA Analysis)

Treatment	Total N	Visit	Mean	Std Dev	90% CI (ms)
CPX-351	20	Day 1- 4 hours post start of infusion	8.0	11.7	(3.5, 12.6)

D=Day, Std Dev=Standard Deviation, CI=confidence interval (not model-based).

Only the therapeutic dose (100 unit/m^2) was studied in this study, which is close to the MTD dose (101 unit/m^2). As there is no formal DDI study conducted, the potential from concomitant medicine is unknown. In addition, although based on the population PK analysis, no significant difference in clearance of cytarabine or daunorubicin was observed in patients with mild to moderate renal impairment, the mass balance study showed that 80% radioactive labeled cytarabine is recovered from urine, mostly as metabolite Ara-U (arabinofuranosyluracil). Thus, higher concentrations of metabolite may not be ruled out for renal impairment scenario and this could be a potential worst case scenario. Such worst case scenario exposure may not be covered, but the study was done almost at MTD dose and higher doses may not be feasible.

2 PROPOSED LABEL

The sponsor included following QT-related language in their current proposed label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

[redacted]

Reviewer's Comment: We don't agree with the sponsor's proposal because the study is not designed to exclude small mean QTc prolongation (i.e., 10 ms). Therefore, we suggest the following labeling language. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

[redacted] At the therapeutic exposures with the recommended dosing regimen of VYXEOS, no large mean changes in the QTc interval (i.e., >20 ms) were detected in the study. An exposure-QTc analysis suggested no concentration-dependent QTc interval prolongation.

Reference ID: 4112723

3 BACKGROUND

3.1 PRODUCT INFORMATION

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. (b) (4)

3.2 MARKET APPROVAL STATUS

CPX-351 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

No stand-alone safety pharmacology studies were conducted with CPX-351. Safety pharmacology parameters were included as part of the repeat-dose toxicology studies in rat (Study 1005-0361) and dog (Study 1005-0372). Although the safety pharmacology assessment was confounded by severed toxicities, no unexpected central nervous system or cardiovascular safety signals were evident. Overall, the safety pharmacology assessment did not identify risks to the major vital organ systems other than those known for cytarabine and daunorubicin.

3.4 PREVIOUS CLINICAL EXPERIENCE

Cytarabine causes bone marrow suppression with leukopenia, thrombocytopenia and anemia and less serious gastrointestinal disturbances, oral ulceration and hepatic dysfunction. Daunorubicin may cause myelosuppression and potentially fatal congestive heart failure either during therapy or months to years later. On extravasation, daunorubicin may cause severe local tissue necrosis.

Additional side effects include gastrointestinal disturbances, mucositis, reversible alopecia and rash. Acute infusion-associated reactions (e.g., flushing, shortness of breath, headache, chills, back pain, tightness in the chest and/or hypotension) which resolve once the infusion is terminated, and potential copper associated toxicities (intravascular hemolysis, coma, diarrhea, hematuria, hepatotoxicity, hypotension, jaundice and vomiting) have been noted in large clinical trials of patients receiving liposomal chemotherapeutic agents.

Toxicities observed with CPX-351:

Of the dose-limiting toxicities possibly related to drug observed at 134 units/m2 of CPX-351, one patient experienced a hypertensive crisis, a second patient was observed to have decreased left ventricular function, and the third patient had persistent hypocellularity beyond Study Day 56 (with absolute neutrophil count <1000 and persistence of platelet transfusions).

Two serious adverse events of cardiac toxicity were reported as possibly related to CPX-351. One patient experienced decreased left ventricular function on study Day 26 at 134

Reference ID: 4112723

units/m2 of drug, possibly due to lifetime anthracycline exposure (daunorubicin 369 mg/m2 received pre-study + 177 mg/m2 daunorubicin received with CPX-351). Vancomycin-resistant enterococcal bacteremia was thought to be the main contributor to the myocardial depression because left ventricular ejection fraction recovered to within 5% of baseline values 3 wks later after recovery from the infection. However, a contribution by the study drug to this event could not be ruled out. Another patient who received 2 courses of treatment at 101 units/m2 experienced an episode of orthopnea. At baseline, this patient had substantial prior anthracycline exposure (equivalent to 700 mg/m2 of daunorubicin) and evidence of impaired cardiac function at baseline. This patient recovered after receiving supportive care for congestive heart failure. Given these two cardiotoxic findings, the sponsor recommends that all patients treated with CPX-351 limit the lifetime exposure to anthracyclines to 500 mg/m2 , including the daunorubicin received via CPX-351 during first induction. Thereafter, decisions about subsequent course of treatment can be based upon evidence of antileukemic effect and evidence of cardiac changes following initial exposure to CPX-351.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of CPX-351's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 72,939. The sponsor submitted the study report CLTR0310-206 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

An Open Label Phase 2 Pharmacokinetic and Pharmacodynamic Assessment of the Potential for QTc Prolongation following First Induction Treatment with CPX-351 (Cytarabine:Daunorubicin) Liposome Injection in Acute Leukemias and MDS Patients

4.2.2 Protocol Number

CLTR0310-206

4.2.3 Study Dates

Study Initiated: 08 August 2014 (first subject enrolled)

Study Completed: 21 January 2016 (last subject completed)

4.2.4 Objectives

Primary Objective: To assess the effect of CPX-351 on cardiac repolarization following the first induction cycle of CPX-351 as determined by Fridericia's corrected QT-interval (QTcF).

Reference ID: 4112723

Secondary Objectives:

- To assess the effects of CPX-351 on cardiac repolarization following the first induction cycle of CPX-351as determined by QT/QTc.
- To obtain serum copper pharmacokinetics (PK) in all subjects receiving CPX-351.
- To obtain total plasma PK data for cytarabine and daunorubicinol following administration of CPX-351 and to correlate changes in QTcF with plasma concentrations of those drugs and their metabolites.
- To evaluate the total and encapsulated cytarabine and daunorubicin plasma concentrations in subjects receiving CPX-351.
- To collect efficacy data (complete response (CR) and complete response with incomplete platelet recovery (CRi) and safety data (adverse event, serious adverse events, laboratory safety. Incuction mortality at Day 30 and Day 60, and clinical cardiac safety (including electrocardiograms, Cardiac AEs, and left ventricular ejection fraction changes).
- To obtain total urine PK data for cytarabine and daunorubicin and their major metabolites, Ara-U and daunorubicinol, following administration of CPX-351.

4.2.5 Study Description

4.2.5.1 Design

This Phase 2, open-label, single-arm, non-randomized, multicenter study was designed to evaluate the safety, PK, and pharmacodynamics (PD) effects of CPX-351 in subjects with acute leukemia or myelodysplastic syndrome (MDS) who were suitable for treatment with intensive chemotherapy.

The study comprised two phases: a Treatment Phase and a Follow-up Phase. During the Treatment Phase, subjects were eligible to receive up to 2 inductions with CPX-351 and up to 4 consolidations with CPX-351. The number of inductions and consolidations a subject received depended upon response (CR or CRi), which was confirmed by bone marrow assessment. For the first induction, the dose of CPX-351 was 100 units/m^2 administered by 90-minute intravenous (IV) infusion on Days 1, 3, 5. (If the second induction was administrated, the dose of CPX-351 was 100 units/m^2 by 90-minute IV infusion on Days 1 and 3). For consolidation therapy, the dose of CPX-351 was 65 units/m^2 administered by 90-minute IV infusion on Days 1 and 3. The Follow-up Phase began after the completion of the treatment phase, and last 60 days.

After providing written informed consent, eligible subjects were enrolled into the study. Within 48 hours of enrollment, subjects began a first induction course. At specific time points during the first induction course, subjects underwent cardiac repolarization assessments, and PK assessments for cytarabine, daunorubicin and serum copper. Throughout the study, subjects were monitored for safety. Serious AEs were reported from the start of the first study infusion to 30 days after completion of the study period.

4.2.5.2 Controls

No placebo and positive (moxifloxacin) controls in this submission.

Reference ID: 4112723

4.2.5.3 Blinding

CPX-351 was administrated in an open-label manner.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

CPX-351 at 100u/m^2 administered on study days 1, 3, and 5 by 90 minute infusion.

4.2.6.2 Sponsor's Justification for Doses

Two different doses of CPX-351 were used in this study: 100 units/m2 CPX-351 was used for all induction courses and 65 units/m^2 was used for all consolidation courses. The induction dose used in this study (100 units/m^2 CPX-351) approximates the maximally tolerated dose defined in the Phase 1 Study 101 conducted in previously treated AML subjects. In Study 101, 101 units/m^2 CPX-351 resulted in persistences of 5:1 molar ratio of cytarabine:daunorubicin in plasma for up to 24 hours after dosing, as well as anti-leukemic activity. The intensity of consolidation with CPX-351 was reduced from that used in previous studies(ie, from 3 to 2 doses and from 100 units/m2 to 65 units/m2) to match the condolidations used with standard of care treatment.

Reviewer's Comment: Acceptable for characterizing the QTc at the therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

No food effects on PK are expected as CPX-351 was administrated by IV infusion.

4.2.6.4 ECG and PK Assessments

PK Assessment:

CPX-351 was administered at 100 units/m^2 by 90-minute IV infusion followed by a flush on Days 1, 3, and 5. Plasma PK samples for cytarabine, daunorubicin, Ara-U, and daunorubicinol were collected after the Day 1 and Day 5 doses from all subjects at the following times:

- Induction 1, Day 1: Pre-dose and at the following times after the start of infusion (SOI): 45 and 90 minutes, and 2, 4, 6, 8, and 24 hours.
- Induction 1, Day 5: Pre-dose and at the following times after the SOI: 45 and 90 minutes, and 2, 4, 6, 8, 24, 28, 48, 72, 96, 168, 216, 336, and 384 hours.

Plasma PK samples collected from all subjects (Groups A and B) were processed for total concentrations of the parent drugs and their respective metabolites, and the plasma samples collected from Group B subjects underwent additional processing to enable determination of concentrations of free cytarabine and daunorubicin.

ECG Assessment:

Triplicate 12-lead ECGs were extracted from Holter recordings spanning Study Days 0, 1, and 5-7 at predose and at up to 9 time points after the SOI. The time points on each Study Day allowed for time-matched comparisons from Study Days 1 through 7 to Day 0. Single 12-lead ECGs were collected on Study Days 8, 9, 12, 14, 19, 21, 60 and either at the end of study (EOS) or early termination (ET).

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- Induction 1, Day 0: Extractions performed at the same relative time points to the Day 1 infusion
- Induction 1, Day 1: pre-dose, and at the following time points after the SOI: 45 and 90 minutes and 2, 3, 4, 6, 8, 12, and 24 hours
- Induction 1, Day 5: pre-dose, and at the following time points after the SOI: 45 and 90 minutes, and 2, 3, 4, 6, 8, 12, and 24 hours
- Induction 1, Day 6: 26, 28, 32, and 36 hours after the SOI on Day 5
- Induction 1, Day 7: 48 hours after the SOI on Day 5

Conventional 12 lead ECG recordings were performed at the following time points:

- Induction 1, Day 8: 72 hours after the SOI on Day 5
- Induction 1, Day 9: 96 hours after the SOI on Day 5
- Induction 1, Day 12: 168 hours after the SOI on Day 5
- Induction 1, Day 14: 216 hours after the SOI on Day 5
- Induction 1, Day 19: 336 hours after the SOI on Day 5
- Induction 1, Day 21: 384 hours after the SOI on Day 5
- Within 30 days after EOS or ET
- 60 Days (± 10) Post EOS.

Reviewer's Comment: Acceptable. The ECG/PK timing is reasonable to capture the effects of all components of CPX-351 and its metabolites near their T_{max} (cytarabine ~1.75 h, its metabolite Ara-U ~24 h, daunorubicin ~2 h and its metabolite daunorubicinol ~48 h) and also capture any potential delayed effects up to 48 h.

4.2.6.5 Baseline

Sponsor used time-matched QTc values on Day 0 as baseline.

4.2.1 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.2 Sponsor's Results

4.2.2.1 Study Subjects

All 26 subjects participate in PK/PD evaluations after receiving the first induction treatment of CPX-351. Twenty-three subjects completed QT/QTc evaluations. Eleven subjects completed the 60-day Follow-up visit. Subject disposition is illustrated below in Figure 1.

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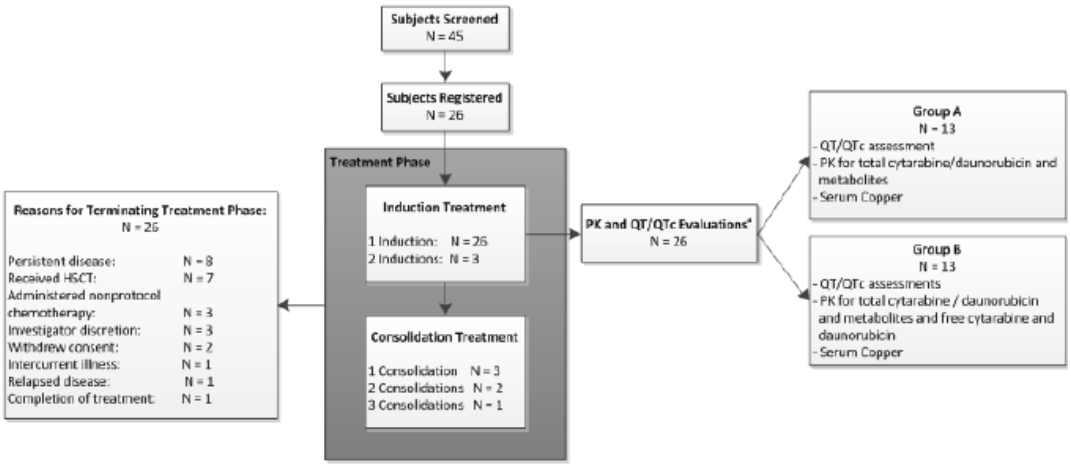
Figure 1: Subject Disposition



Abbreviations: HSCT = hematopoietic stem cell transplant; PK = pharmacokinetics; QT = QT interval; QTc = corrected QT interval

[a] Six subjects received 24-hour urine sampling for 5 days following the end of infusion on Day 5 of the first induction

Source: Table 14.1.6 and Table 14.3.8.1

Source: Clinical Study Report CLTR0310-206, Figure 1, Page 28/392.

4.2.2.2 Statistical Analyses

4.2.2.2.1 Primary Analysis

The primary endpoint is time-matched change from baseline in QTcF. The sponsor's central tendency analysis result is shown in Figure 2.

The largest change from baseline QTcF were observed 4 hours after the SOI (start of infusion) on Day 1 with the upper limit of the 1-sided 95% CI reaching 12.3 ms (mean [SD], 8.0 ms [11.69 ms]). Similar increases were observed 3 hours on Day 1, with the upper bound of the 1-sided 95% CI reaching 10.7 ms (mean [SD], 5.3 [15.17] ms). No other upper limits of the 95% CIs crossed the 10 ms threshold at any timepoint.

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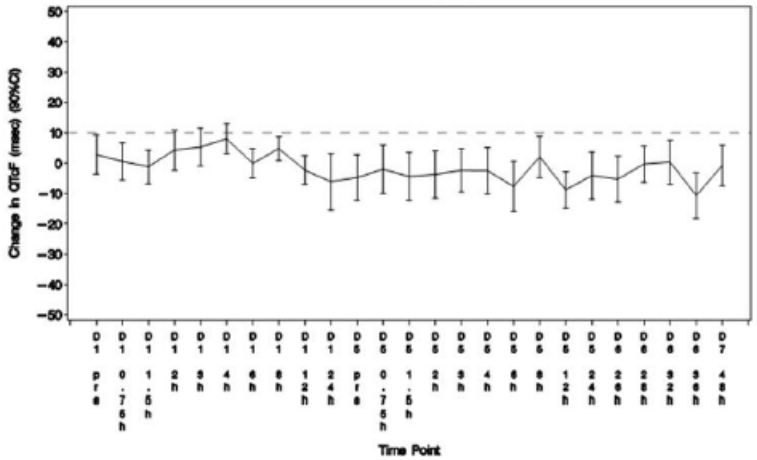
Figure 2: Sponsor's Mean (90%CI) Change from Baseline in QTcF by Time Point (ECG Population)



Abbreviations: CI = confidence interval; ECG = electrocardiogram; QTcF = Fridericia's corrected QT-interval.
Note that the upper limit of the 2-sided 90% CI is the same quantity as the upper limit for a 1-sided 95% CI.
Source: Study 206 Cardiac Safety Report, Figure 1.

Reviewer's Comments: We provide our independent analysis result in Section 5.2. Our results are similar as those reported by the sponsor.

4.2.2.2.1 Assay Sensitivity

No applicable.

4.2.2.2.2 Categorical Analysis

No subjects had QTcF > 480 ms or ΔQTcF > 60 ms.
Reviewer's Comments: We provide our independent analysis result in Section 5.2. Our results are similar as those reported by the sponsor.

4.2.2.2.3 Additional Analyses

No clinically important effect of CPX-351 on HR, PR and QRS intervals were observed.

4.2.2.3 Safety Analysis

A total of 5 deaths were reported during the study, and the primary cause of death was progressive AML. None of the deaths were considered related to study drug. No deaths occurred during the Treatment Phase; all deaths occurred during the Follow-up Phase. Two subjects experienced Grade 5 SAEs leading to death (Sepsis and AML recurrent).

All subjects experienced AEs during the study, and all subjects experienced AEs considered to be related to treatment. No subjects had AEs leading to discontinuation of study drug. A total of 8/26 (30.8%) subjects experienced SAEs. Two subjects experienced Grade 5 events, neither of which occurred during the Treatment Period.

The SOCs with the highest number of reported AEs were General Disorders and Administration Site Conditions (24/26 subjects, 92%) and Respiratory. Thoracic and Mediastinal Disorders (24/26 subjects, 92%). The most frequency reported AEs were Febrile Neutropenia (19/26 subjects, 73%). Fatigue (14/26 subjects, 54%), and Nausea (14/26 subjects, 54%).

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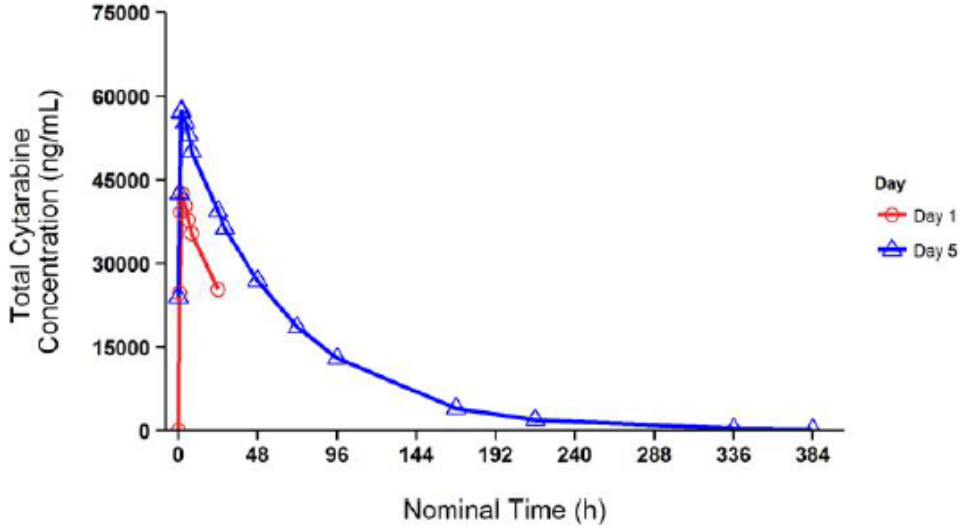
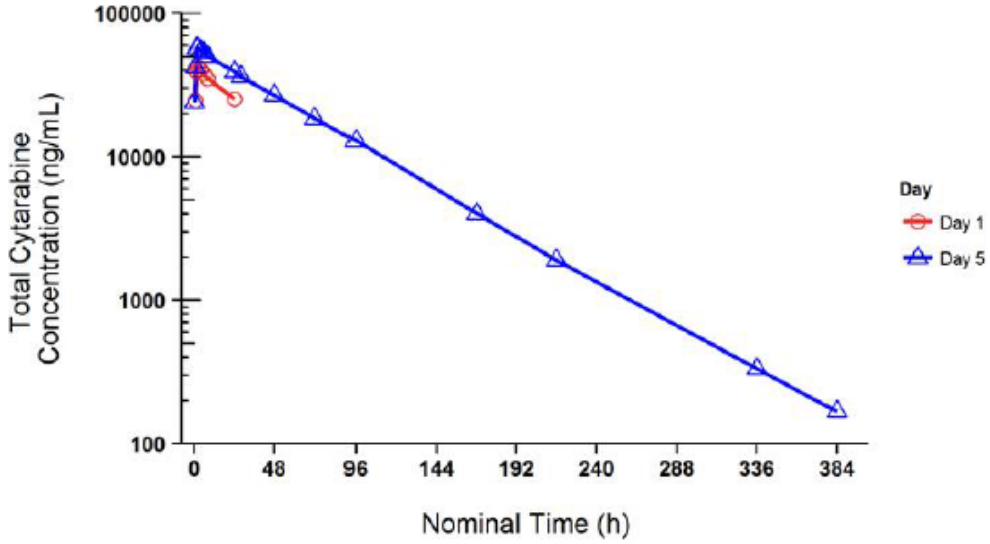
4.2.2.4 Clinical Pharmacology

4.2.2.4.1 Pharmacokinetic Analysis

Figure 3: Mean Total Cytarabine Plasma Concentration vs. Time Plot on Day 1 and Day 5 (Linear and Semi-log Scale), (N = 26)





Reference ID: 4112723

Figure 4: Mean Total, Encapsulated, and Free Cytarabine Plasma Concentration vs. Time Plot on Day 1 (Linear and Semi-log Scale)

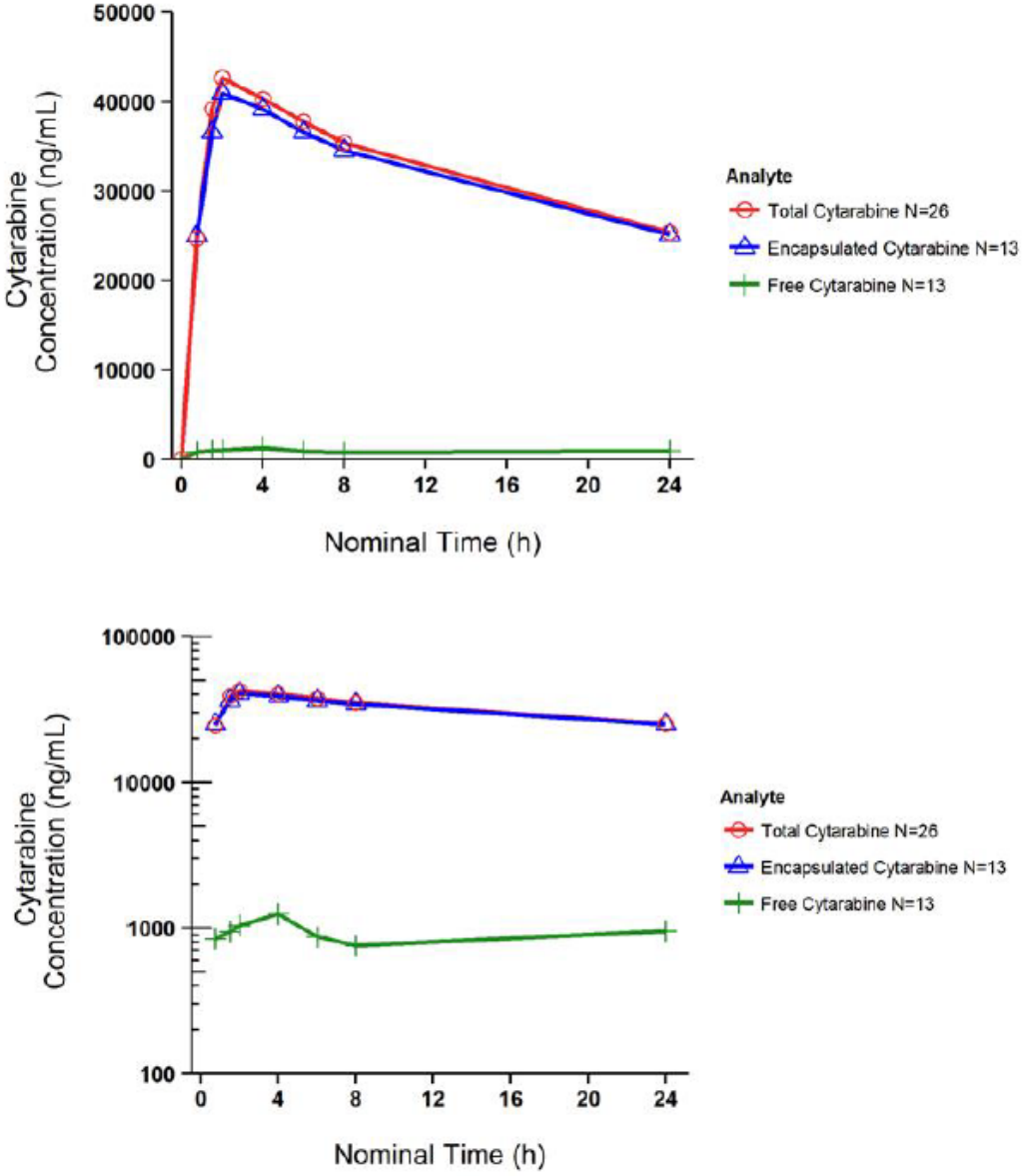
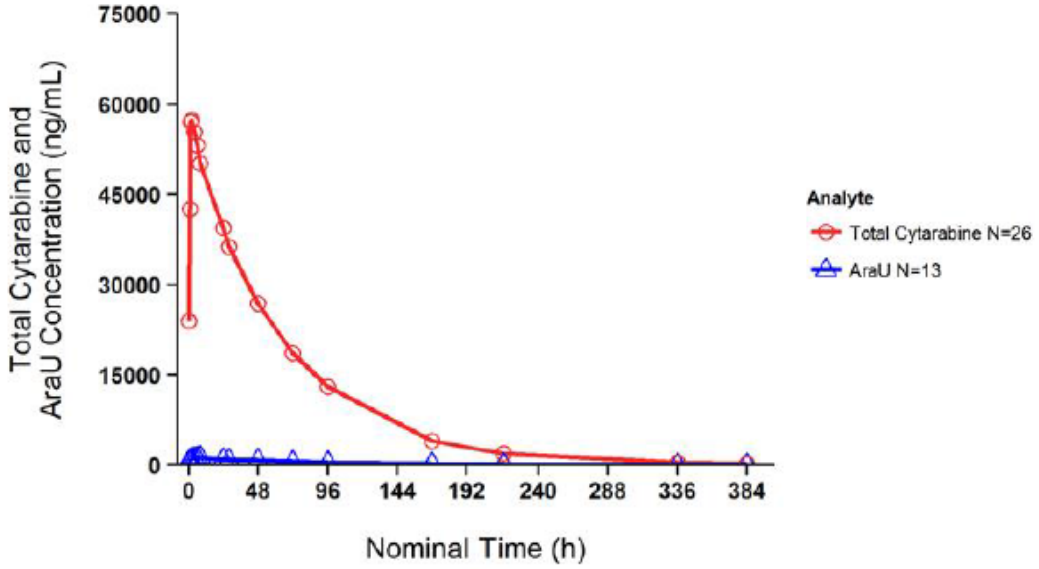
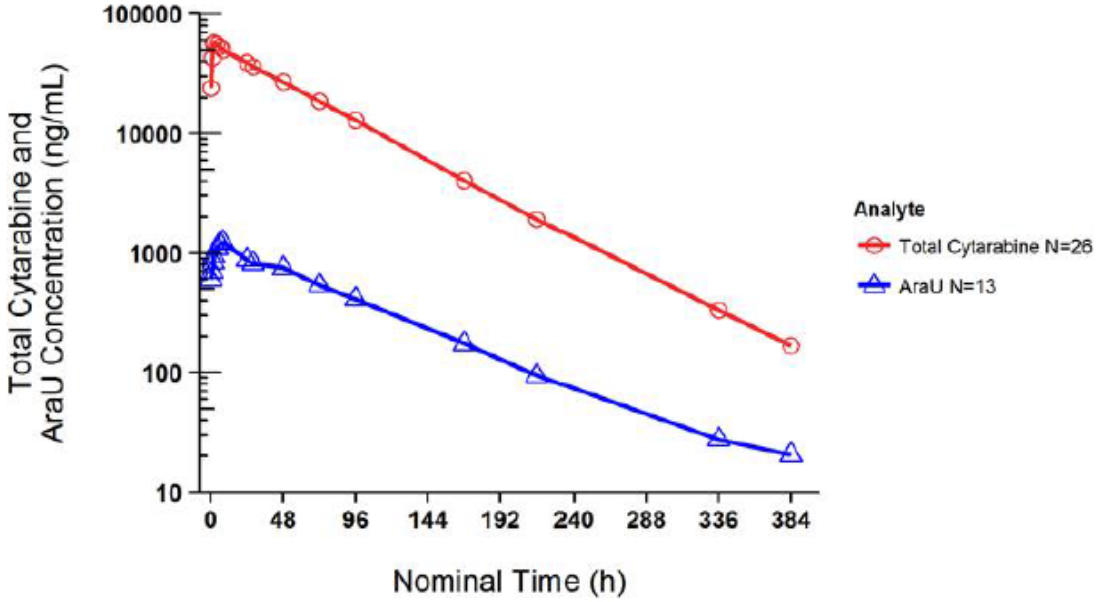


Figure 5: Mean Total Cytarabine and Ara-U Plasma Concentration vs Time Plot on Day 5 (Linear and Semi-log Scale)





Reference ID: 4112723

Figure 6: Mean Total Daunorubicin Plasma Concentration vs Time Plot on Day 1 and Day 5 (Linear Scale)

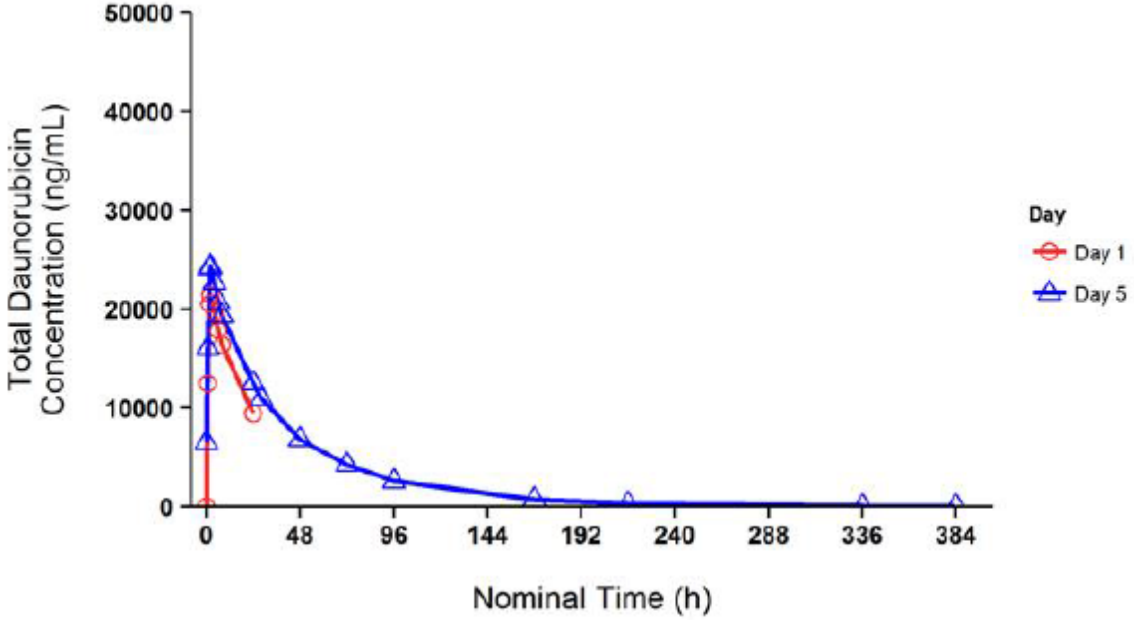
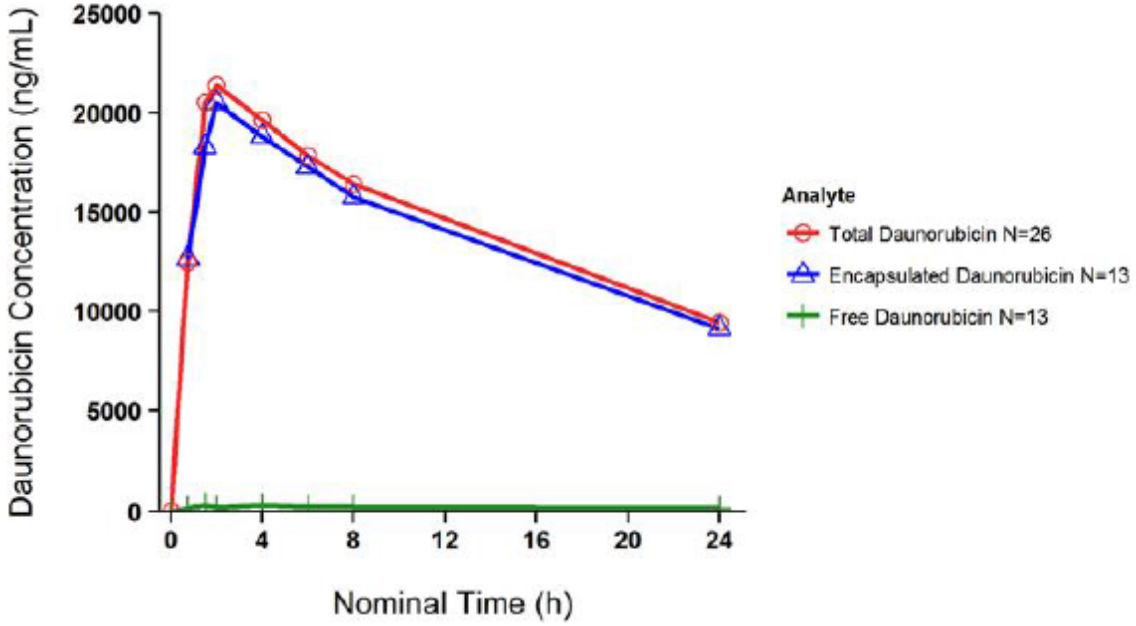
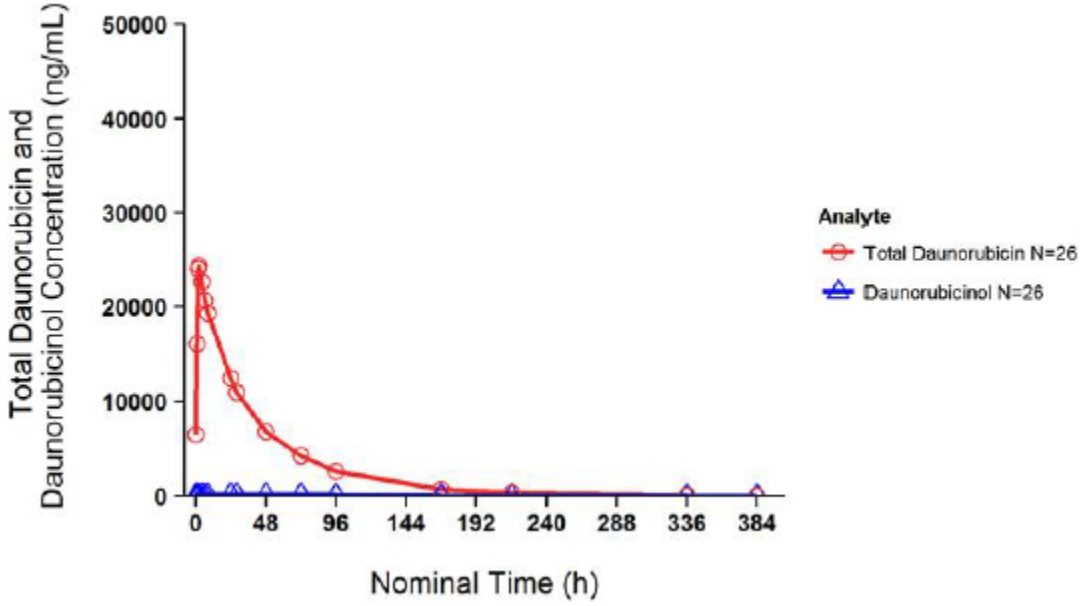


Figure 7: Mean Total, Encapsulated, and Free Daunorubicin Plasma Concentration vs Time Plot on Day 1 (Linear Scale)



Reference ID: 4112723

Figure 8: Mean Total Daunorubicin and Daunorubicinol Plasma Concentration vs Time Plot on Day 5 (Linear Scale)



The PK results are presented below:

Table 2: Plasma Pharmacokinetic Parameters for Total Cytarabine on Day 1

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUC48 (h*ng/mL)	AUClast (h*ng/mL)
N	26	26	26	15	26
Mean	NC	46000	765000	1110000	765000
SD	NC	12600	216000	344000	217000
CV%	NC	27.3	28.3	31.0	28.3
Geo Mean	NC	44500	735000	1060000	735000
Geo CV%	NC	27.5	29.9	33.1	29.9
Median	2.01	44800	759000	1060000	760000
Min	0.78	27000	395000	533000	395000
Max	6.07	80300	1220000	1910000	1220000

NC = Not calculated

Reference ID: 4112723

Table 3: Plasma Pharmacokinetic Parameters for Total Cytarabine on Day 5

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUCtau (h*ng/mL)	CLss (L/h)	Vz (L)	t½ (h)	RaccAUCtau
N	26	26	26	26	26	26	26	15
Mean	NC	62200	1130000	1900000	0.131	7.11	40.4	1.39
SD	NC	20900	441000	844000	0.0791	3.50	9.77	0.428
CV%	NC	33.7	39.2	44.3	60.2	49.2	24.2	30.7
Geo Mean	NC	58900	1040000	1710000	0.113	6.38	39.1	1.33
Geo CV%	NC	34.6	44.5	52.8	58.1	50.0	28.0	36.0
Median	2.00	62100	1150000	1970000	0.104	6.03	42.5	1.37
Min	0.75	35000	432000	596000	0.0511	2.14	19.1	0.535
Max	8.33	111000	2240000	4110000	0.324	16.5	57.6	2.13

NC = Not calculated
Racc = Accumulation Ratio

Table 4: Plasma Pharmacokinetic Parameters for Encapsulated Cytarabine on Day 1

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUC48 (h*ng/mL)	AUClast (h*ng/mL)
N	13	13	13	10	13
Mean	NC	45300	747000	1200000	747000
SD	NC	14800	222000	358000	222000
CV%	NC	32.6	29.8	29.7	29.7
Geo Mean	NC	43200	716000	1150000	716000
Geo CV%	NC	32.6	31.3	35.5	31.3
Median	2.03	42500	729000	1200000	730000
Min	0.78	26700	384000	520000	384000
Max	6.07	77600	1180000	1790000	1180000

NC = Not calculated.

Table 5: Plasma Pharmacokinetic Parameters for Free Cytarabine on Day 1

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUC48 (h*ng/mL)	AUClast (h*ng/mL)
N	13	13	13	1	13
Mean	NC	1850	20800	35500	20800
SD	NC	989	7930	NC	7950
CV%	NC	53.6	38.1	NC	38.1
Geo Mean	NC	1670	19600	NC	19700
Geo CV%	NC	47.0	35.9	NC	35.9
Median	2.28	1620	20400	NC	20400
Min	0.78	928	10900	NC	10900
Max	24.03	4540	41500	NC	41600

NC = Not calculated

Reference ID: 4112723

Table 6: Plasma Pharmacokinetic Parameters for Ara-U on Day 1

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUClast (h*ng/mL)	M:P Ratio Cmax (%)	M:P Ratio AUC (%)
N	13	13	13	13	13	13
Mean	NC	710	13500	13500	1.70	2.00
SD	NC	214	3480	3490	0.881	1.21
CV%	NC	30.2	25.9	25.9	51.9	60.6
Geo Mean	NC	685	13100	13100	1.53	1.77
Geo CV%	NC	27.1	24.2	24.3	47.3	50.6
Median	8.03	679	12800	12800	1.41	1.82
Min	7.93	473	9400	9400	0.844	0.882
Max	24.03	1310	22300	22300	4.12	5.62

NC = Not calculated

M:P = Metabolite to Parent Ratio as a %.

Table 7: Plasma Pharmacokinetic Parameters for Ara-U on Day 5

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUCtau (h*ng/mL)	AUClast (h*ng/mL)	t½ (h)	M:P Ratio Cmax (%)	M:P Ratio AUC (%)
N	13	13	13	13	13	13	13	13
Mean	NC	1240	25000	44000	104000	60.3	2.26	3.22
SD	NC	252	5670	11300	43800	15.6	0.865	1.47
CV%	NC	20.3	22.7	25.6	42.1	25.9	38.2	45.8
Geo Mean	NC	1220	24500	42700	94700	58.2	2.11	2.99
Geo CV%	NC	18.1	19.7	25.0	49.2	30.0	40.6	40.3
Median	8.00	1150	24200	43700	101000	65.6	2.20	2.85
Min	5.78	991	18800	25800	39400	32.5	1.12	1.64
Max	8.33	1960	41900	73400	184000	82.0	3.93	7.39

NC = Not calculated

M:P = Metabolite to Parent Ratio as a %.

Table 8: Plasma Pharmacokinetic Parameters for Total Daunorubicin on Day 1 and Day 5

Day 1

Statistic	Parameter				
	T_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	AUC_{48} (h*ng/mL)	AUC_{last} (h*ng/mL)
N	26	26	26	25	26
Mean	NC	23100	340000	499000	340000
SD	NC	6590	87900	144000	88000
CV%	NC	28.5	25.9	28.9	25.9
Geometric Mean	NC	22300	328000	477000	329000
Geometric CV%	NC	27.8	27.6	32.3	27.6
Median	2.00	22200	335000	498000	335000
Min	0.78	13600	179000	219000	179000
Max	4.37	42400	524000	732000	524000

Day 5

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Statistic	Parameter							
	T_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	AUC_{tau} (h*ng/mL)	CLss (L/h)	Vz (L)	$t_{1/2}$ (h)	RaccAUCtau
N	26	26	26	26	26	26	26	25
Mean	NC	26000	415000	637000	0.163	6.64	31.5	1.26
SD	NC	8510	140000	244000	0.0868	2.44	9.00	0.302
CV%	NC	32.7	33.6	38.4	53.3	36.8	28.5	23.9
Geo Mean	NC	24900	391000	588000	0.145	6.28	30.0	1.22
Geo CV%	NC	30.9	37.6	44.6	50.3	33.9	35.3	29.0
Median	2.00	24600	429000	652000	0.138	5.94	32.2	1.28
Min	0.75	15900	186000	238000	0.0762	3.78	11.8	0.495
Max	6.02	53800	715000	1210000	0.372	14.2	47.9	1.75

Table 9: Plasma Pharmacokinetic Parameters for Encapsulated and Free Daunorubicin on Day 1

Encapsulated

Statistic	Parameter				
	T_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	AUC_{48} (h*ng/mL)	AUC_{last} (h*ng/mL)
N	13	13	13	12	13
Mean	NC	22600	328000	476000	312000
SD	NC	7660	93700	150000	110000
CV%	NC	34.0	28.6	31.4	35.4
Geometric Mean	NC	21500	316000	453000	292000
Geometric CV%	NC	31.3	29.7	35.0	41.7
Median	2.00	20600	324000	448000	296000
Min	0.78	13800	177000	216000	117000
Max	4.37	41800	517000	720000	517000

Free

Statistic	Parameter				
	T_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	AUC_{48} (h*ng/mL)	AUC_{last} (h*ng/mL)
N	13	13	12	0	13
Mean	NC	522	4760	NC	4500
SD	NC	529	1760	NC	1930
CV%	NC	101	37.0	NC	42.8
Geometric Mean	NC	391	4480	NC	4100
Geometric CV%	NC	78.1	37.6	NC	50.6
Median	3.97	281	4680	NC	4640
Min	0.78	238	2170	NC	1380
Max	24.03	1890	9010	NC	9010

Table 10: Plasma Pharmacokinetic Parameters for Daunorubicinol on Day 1 and Day 5

Day 1

Reference ID: 4112723

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUClast (h*ng/mL)	M:P Ratio Cmax (%)	M:P Ratio AUC (%)
N	26	26	26	26	26	26
Mean	NC	36.6	690	690	0.165	0.210
SD	NC	6.17	110	110	0.0406	0.0394
CV%	NC	16.9	15.9	16.0	24.6	18.8
Geo Mean	NC	36.0	680	681	0.161	0.207
Geo CV%	NC	18.8	17.3	17.4	23.3	18.5
Median	24.00	37.0	709	709	0.154	0.197
Min	0.78	21.8	397	397	0.104	0.155
Max	24.12	45.6	972	973	0.271	0.294

NC = Not calculated

M:P = Metabolite to Parent Ratio as a %

Day 5

Statistic	Tmax (h)	Cmax (ng/mL)	AUC24 (h*ng/mL)	AUCtau (h*ng/mL)	AUClast (h*ng/mL)	t½ (h)	M:P Ratio Cmax (%)	M:P Ratio AUC (%)
N	26	26	26	26	26	26	26	26
Mean	NC	147	2880	6240	17900	43.9	0.570	1.79
SD	NC	52.3	948	2270	9350	10.7	0.168	0.443
CV%	NC	35.7	32.9	36.4	52.2	24.4	29.4	24.8
Geo Mean	NC	136	2710	5790	15100	42.7	0.545	1.73
Geo CV%	NC	43.1	38.4	44.0	73.0	24.1	32.3	25.7
Median	26.24	144	2910	6150	18000	43.2	0.589	1.82
Min	1.50	52.8	1160	2170	3240	26.9	0.257	1.15
Max	48.00	227	4410	9840	41400	70.2	0.966	2.59

NC = Not calculated

M:P = Metabolite to Parent Ratio as a %

4.2.2.4.2 Exposure-Response Analysis

The relationship between ΔQTc and the plasma concentrations were investigated by linear mixed-effects modeling based on the PK/ΔQTc analysis set. It was assumed a priori that the relationship between plasma concentration and the natural logarithm of ΔQTc was linear. A random effects model was run using both intercept and slope as random effects as well as a random subject effect. Concentration-response analysis did not show an increase in the QTcF with increased exposure to the components of CPX-351 or its metabolites. None of the slope estimates were statistically significant from zero.

The Cmax for CPX-351 was between 2 and 4 hours after the start of infusion, which corresponds with the Cmax reported and with the peak time of ΔQTcF and ΔQTcB. Therefore, no hysteresis assessments were needed.

Reference ID: 4112723

Figure 9: Change from baseline QTcF vs log(Ara-U) Plasma Concentrations

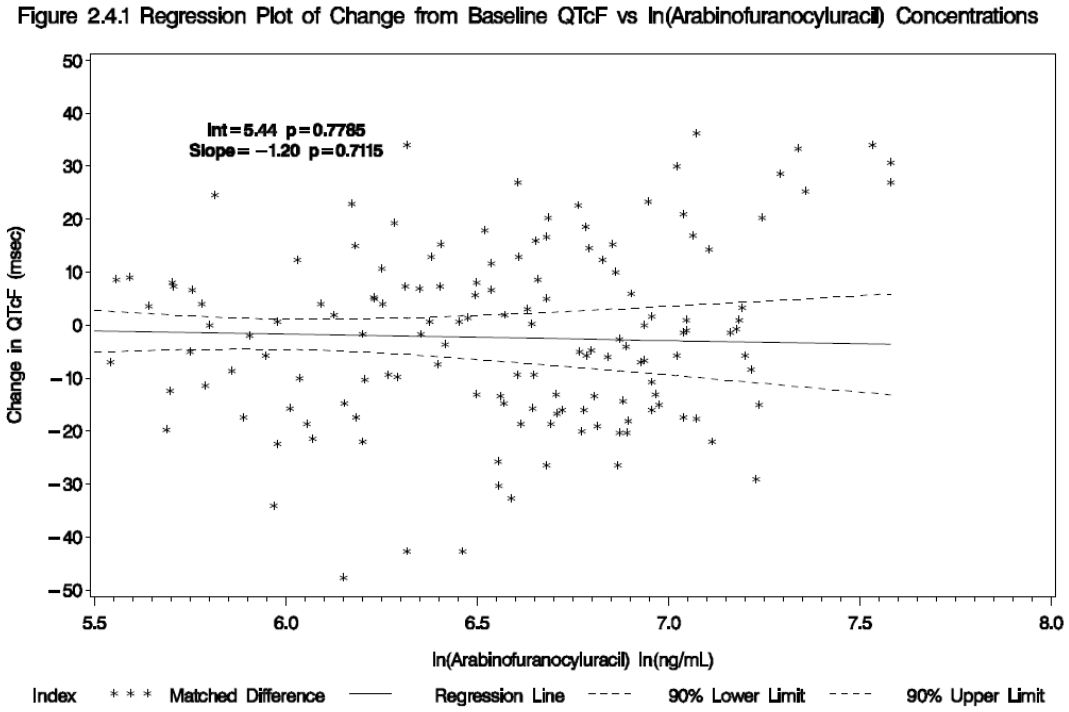
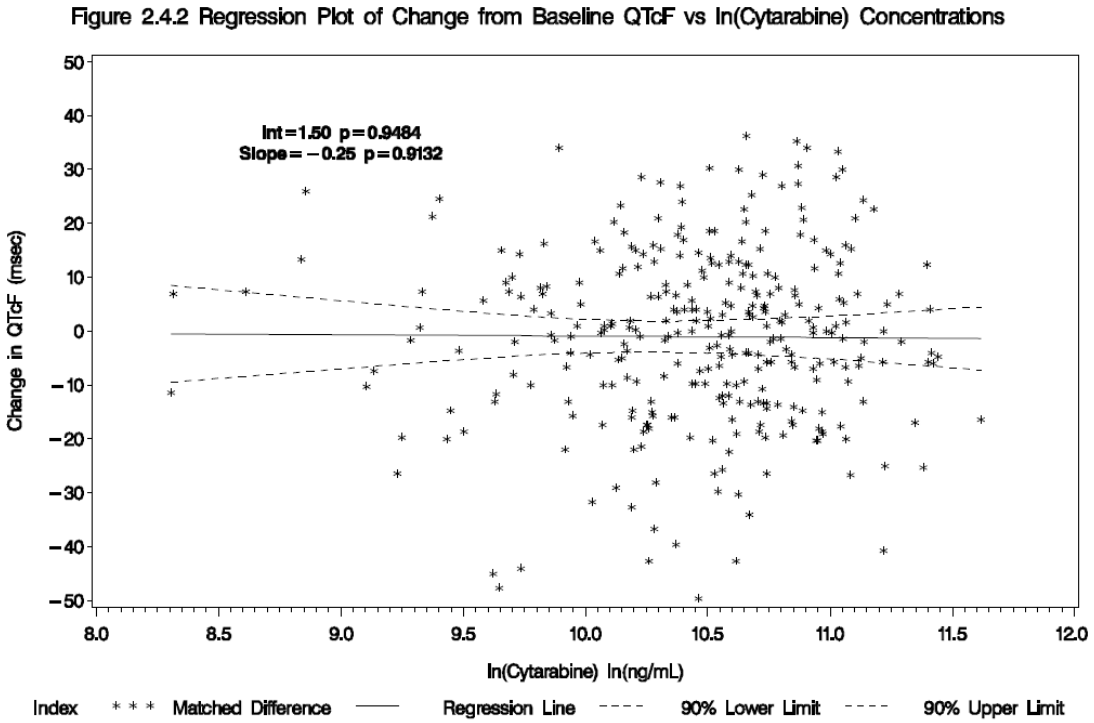


Figure 10: Change from baseline QTcF vs log(Cytarabine) Plasma Concentrations



Reference ID: 4112723

Figure 11: Change from baseline QTcF vs log(Daunorubicin) Plasma Concentrations

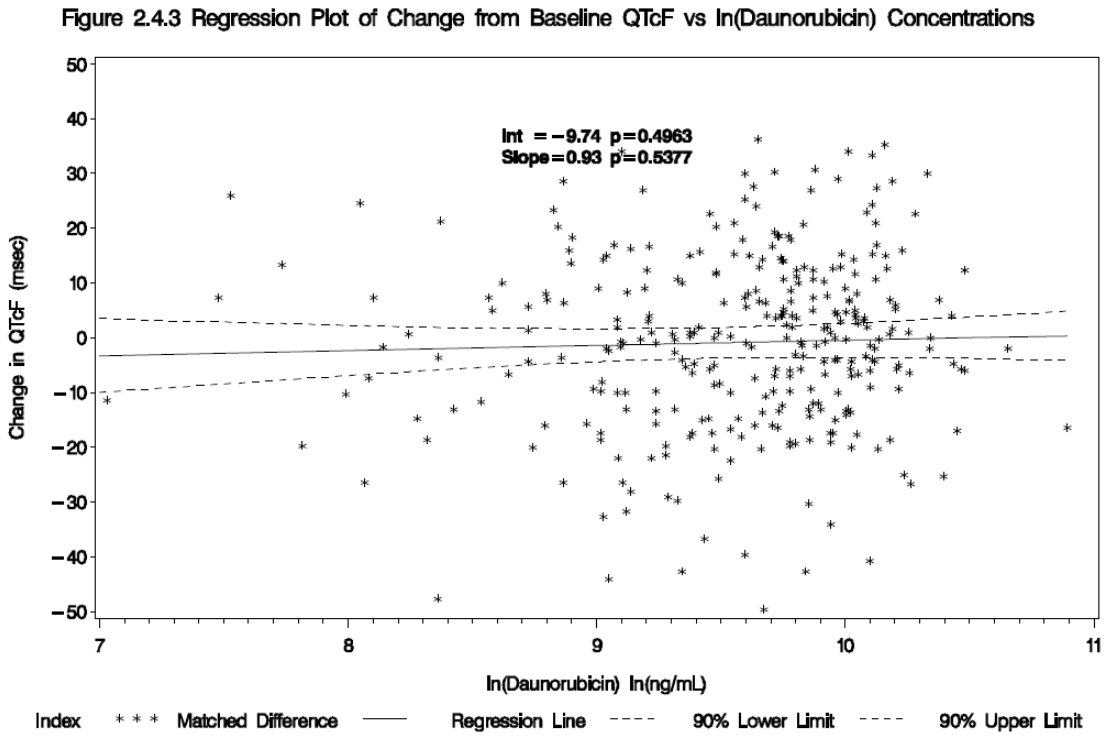
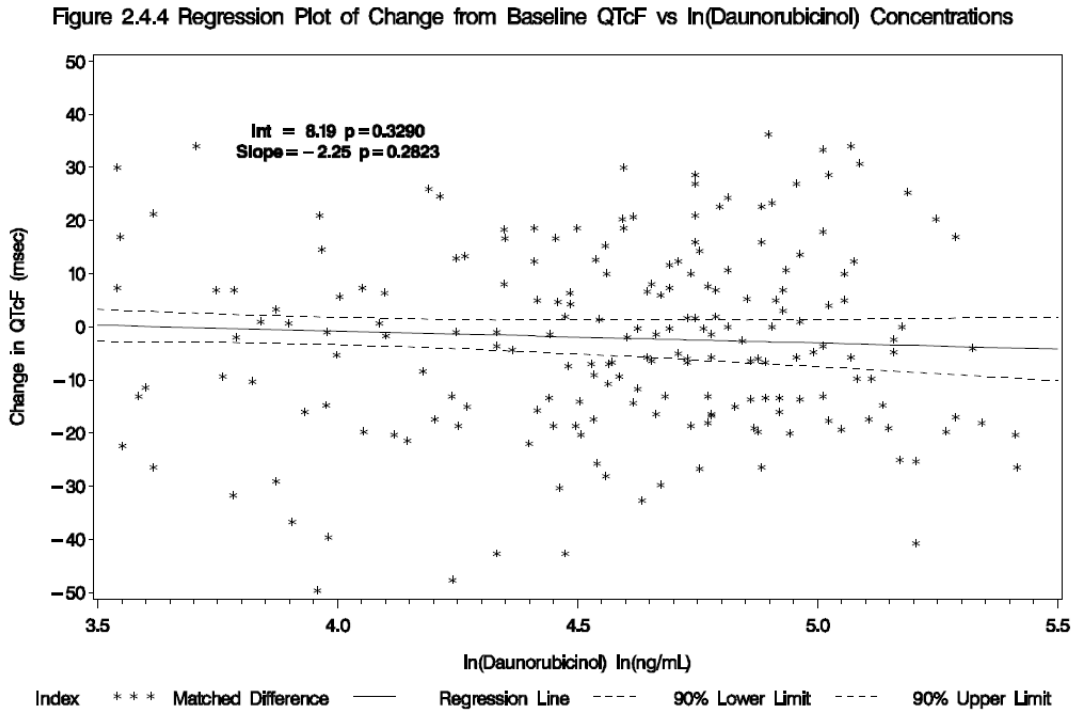


Figure 12: Change from baseline QTcF vs log(Daunorubicinol) Plasma Concentrations



Reference ID: 4112723

Figure 13: Change from baseline QTcF vs log(Free Cytarabine) Plasma Concentrations

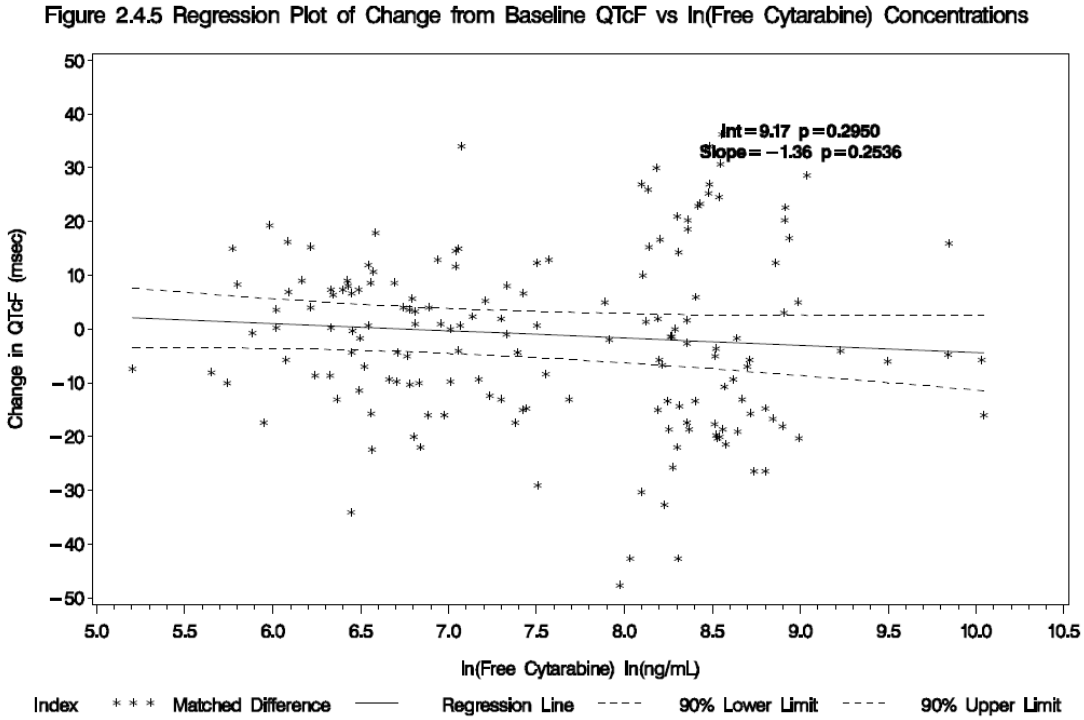
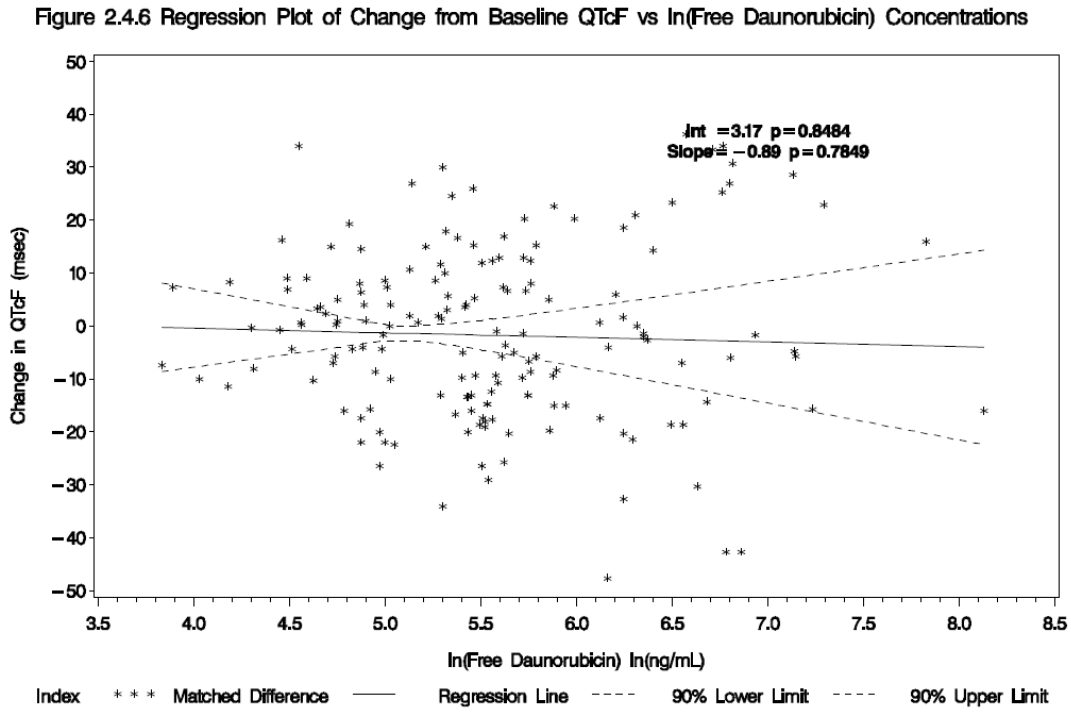


Figure 14: Change from baseline QTcF vs log(Free Daunorubicin) Plasma Concentrations



Reference ID: 4112723

Reviewer's Analysis: An independent reviewer's analysis is presented in Section 5.3. Our results are similar as those reported by the sponsor.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate QT/RR correction method because the sponsor provided QTcB and QTcF correction intervals. QTcF was chosen for the primary statistical analysis and C-QTc analysis.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for CPX-351

The primary endpoint is the change from baseline of QTcF. The descriptive statistics are listed in Table 11. Table presents the summary statistics (mean and standard deviation) and the 90% confidence interval for mean changes from baseline of CPX-351on Days 1 and 5 (at pre-dose, 45 min., 90 min., and 2, 3, 4, 6, 8, 12, 24 hours post); Day 6 (at 26, 28, 32, and 36 hours post) and Day 7 (at 48 hours post). Using central tendency analysis, the largest upper bound of the 2-sided 90% CI for mean change from baseline in QTcF on Day 1 at 4 hours post is 12.6 ms.

Reference ID: 4112723

Table 11: Analysis Results of ΔQTcF for CPX-351

Visit	N	Mean	Std Dev	90% CI for Mean
D1-Pre	21	2.9	15.4	(-2.9, 8.7)
D1-45min	22	0.6	15.1	(-4.9, 6.2)
D1-90min	21	-1.2	13.3	(-6.2, 3.8)
D1-2h	21	4.3	16.0	(-1.8, 10.3)
D1-3h	21	5.3	15.2	(-0.4, 11.0)
D1-4h	20	8.0	11.7	(3.5, 12.6)
D1-6h	19	-0.1	11.2	(-4.5, 4.4)
D1-8h	17	4.8	8.5	(1.2, 8.4)
D1-12h	18	-2.3	10.4	(-6.6, 2.0)
D1-24h	8	-6.2	13.9	(-15.5, 3.1)
D5-Pre	24	-4.7	19.4	(-11.5, 2.0)
D5-45min	23	-2.0	20.1	(-9.2, 5.2)
D5-90min	20	-4.4	18.5	(-11.6, 2.7)
D5-2h	22	-3.7	19.2	(-10.8, 3.3)
D5-3h	19	-2.4	16.5	(-8.9, 4.2)
D5-4h	19	-2.5	17.6	(-9.5, 4.5)
D5-6h	18	-7.6	18.2	(-15.1, -0.1)
D5-8h	16	2.1	14.5	(-4.2, 8.5)
D5-12h	17	-8.8	13.1	(-14.3, -3.3)
D5-24h	18	-4.1	17.4	(-11.2, 3.0)
D6-26h	21	-5.2	18.0	(-12.0, 1.5)
D6-28h	19	-0.3	13.8	(-5.8, 5.2)
D6-32h	19	0.3	16.5	(-6.2, 6.9)
D6-36h	19	-10.7	17.2	(-17.5, -3.9)
D7-48h	16	-0.8	14.1	(-6.9, 5.4)

D=Day, Std Dev=Standard Deviation, CI=confident interval are not model-based.

5.2.1.2 Assay Sensitivity Analysis

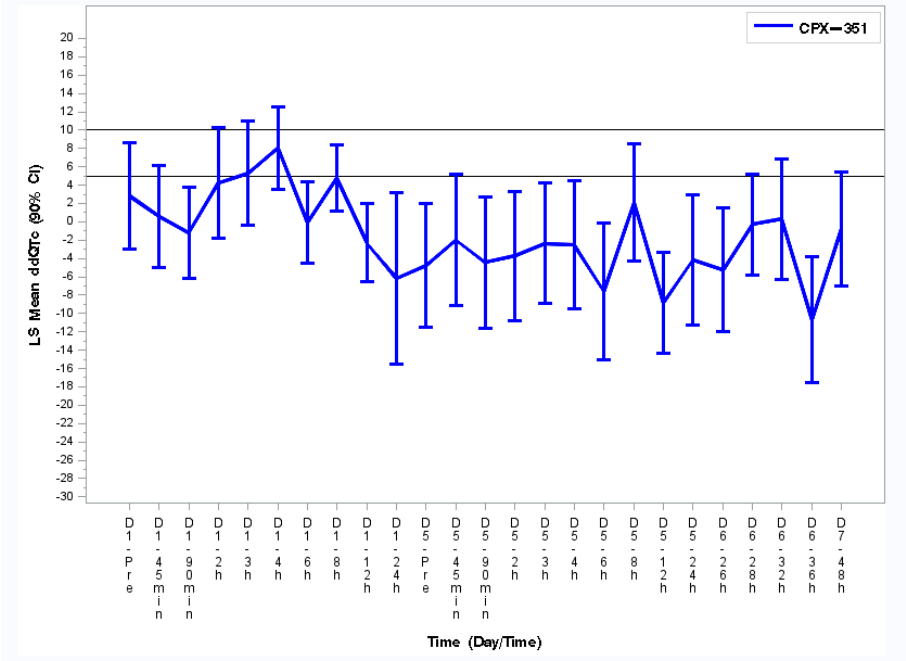
Not applicable.

5.2.1.3 Graph of ΔQTcF Over Time

Figure 15 displays the time profile of ΔQTcF.

Reference ID: 4112723

Figure 15: Mean and 90% CI ΔQTcF Time Profile



5.2.1.4 Categorical Analysis

Table below lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF is above 480 ms.

Table 12: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
CPX-351	26	17 (65.4%)	9 (34.6%)	0 (0.0%)	0 (0.0%)

Table below lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 60 ms.

Table 13: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
CPX-351	25	19 (76.0%)	6 (24.0%)	0 (0.0%)	0 (0.0%)

Reference ID: 4112723

5.2.2 HR Analysis

Using central tendency analysis, the largest upper bound of the 2-sided 90% CI for mean change from baseline of HR on Day 5 at 24 hours post is 12.1 bpm. Table 15 presents the categorical analysis of HR. Sixteen subjects who experienced HR interval greater than 100 bpm are in CPX-351 group.

Table 14: Analysis Results of ΔHR for CPX-351

Visit	N	Mean	Std Dev	90% CI for Mean
D1-Pre	21	-1.9	9.7	(-5.5, 1.8)
D1-45min	22	-3.2	11.5	(-7.4, 1.1)
D1-90min	21	-2.7	10.3	(-6.5, 1.2)
D1-2h	21	-5.3	11.5	(-9.6, -0.9)
D1-3h	21	0.7	9.6	(-2.9, 4.3)
D1-4h	20	-1.1	11.5	(-5.6, 3.3)
D1-6h	19	-0.0	7.5	(-3.0, 3.0)
D1-8h	17	-4.2	10.1	(-8.5, 0.1)
D1-12h	18	2.6	14.4	(-3.3, 8.5)
D1-24h	8	-0.9	5.2	(-4.4, 2.6)
D5-Pre	24	-0.2	18.7	(-6.7, 6.4)
D5-45min	23	-5.0	12.7	(-9.5, -0.5)
D5-90min	20	-7.6	13.0	(-12.7, -2.6)
D5-2h	22	-6.8	11.8	(-11.1, -2.4)
D5-3h	19	-2.0	12.5	(-7.0, 3.0)
D5-4h	19	-0.5	16.7	(-7.2, 6.1)
D5-6h	18	0.9	13.7	(-4.7, 6.5)
D5-8h	16	-10.4	11.4	(-15.4, -5.4)
D5-12h	17	5.9	13.6	(0.1, 11.7)
D5-24h	18	4.0	19.6	(-4.0, 12.0)
D6-26h	21	-0.7	14.3	(-6.0, 4.7)
D6-28h	19	-0.5	16.1	(-6.9, 5.9)
D6-32h	19	-4.4	13.7	(-9.9, 1.0)
D6-36h	19	6.1	14.9	(0.2, 12.1)
D7-48h	16	-2.2	15.9	(-9.2, 4.8)

Reference ID: 4112723

Table 15: **Categorical Analysis of HR**

Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
CPX-351	26	10 (38.5%)	16 (61.5%)

5.2.3 PR Analysis

Using central tendency analysis, the largest upper bound of the 2-sided 90% CI for mean change from baseline in PR on Day 1 after 90 min post is 10.8 ms. Table 17 presents the categorical analysis of PR. Four subjects who experienced PR interval greater than 200 ms are in CPX-351 group.

Table 16: Analysis Results of ΔPR and ΔΔPR for CPX-351

Visit	N	Mean	Std Dev	90% CI for Mean
D1-Pre	21	1.0	11.6	(-3.4, 5.4)
D1-45min	22	3.8	10.0	(0.2, 7.5)
D1-90min	21	7.4	9.2	(3.9, 10.8)
D1-2h	21	3.2	9.2	(-0.3, 6.7)
D1-3h	21	0.7	9.7	(-3.0, 4.4)
D1-4h	20	2.7	9.9	(-1.1, 6.6)
D1-6h	19	2.9	8.0	(-0.3, 6.1)
D1-8h	17	3.4	11.8	(-1.6, 8.4)
D1-12h	18	0.6	10.5	(-3.7, 4.9)
D1-24h	8	2.7	10.3	(-4.2, 9.6)
D5-Pre	24	-3.0	16.5	(-8.8, 2.8)
D5-45min	23	2.0	13.3	(-2.7, 6.8)
D5-90min	20	3.4	15.1	(-2.4, 9.2)
D5-2h	22	1.0	13.8	(-4.1, 6.0)
D5-3h	19	-2.3	17.0	(-9.1, 4.5)
D5-4h	19	-0.5	10.9	(-4.8, 3.8)
D5-6h	18	-0.1	10.8	(-4.5, 4.3)
D5-8h	16	2.1	9.8	(-2.2, 6.4)
D5-12h	17	-4.8	14.3	(-10.8, 1.3)
D5-24h	18	-8.3	19.8	(-16.4, -0.1)
D6-26h	21	-2.8	10.1	(-6.6, 1.0)
D6-28h	19	-5.5	13.4	(-10.8, -0.1)
D6-32h	19	-5.6	15.1	(-11.6, 0.4)

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Visit	N	Mean	Std Dev	90% CI for Mean
D6-36h	19	-5.3	13.3	(-10.6, 0.0)
D7-48h	16	-7.5	18.7	(-15.7, 0.7)

Table 17: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
CPX-351	26	22 (84.6%)	4 (15.4%)

5.2.4 QRS Analysis

Using central tendency analysis, the largest upper bound of the 2-sided 90% CI for mean change from baseline in QRS is 6.0 ms. Table 19 presents the categorical analysis of QRS. Four subjects who experienced QRS interval greater than 110 ms are in CPX-351 group.

Table 18: Analysis Results of ΔQRS for CPX-351

Visit	N	Mean	Std Dev	90% CI for Mean
D1-Pre	21	0.6	4.5	(-1.1, 2.3)
D1-45min	22	-0.1	4.9	(-1.9, 1.7)
D1-90min	21	0.1	5.2	(-1.9, 2.1)
D1-2h	21	0.0	5.1	(-1.9, 1.9)
D1-3h	21	1.1	3.7	(-0.3, 2.5)
D1-4h	20	0.6	5.2	(-1.5, 2.6)
D1-6h	19	-0.2	3.7	(-1.6, 1.3)
D1-8h	17	0.7	4.0	(-1.0, 2.4)
D1-12h	18	0.4	4.6	(-1.5, 2.3)
D1-24h	8	1.2	4.5	(-1.8, 4.2)
D5-Pre	24	1.0	6.2	(-1.2, 3.2)
D5-45min	23	0.8	6.2	(-1.4, 3.0)
D5-90min	20	1.3	5.9	(-0.9, 3.6)
D5-2h	22	0.6	6.3	(-1.8, 2.9)
D5-3h	19	1.7	5.2	(-0.4, 3.7)
D5-4h	19	1.1	6.0	(-1.3, 3.5)
D5-6h	18	0.4	6.0	(-2.0, 2.9)
D5-8h	16	2.3	7.5	(-1.0, 5.6)

Reference ID: 4112723

Visit	N	Mean	Std Dev	90% CI for Mean
D5-12h	17	-0.3	4.7	(-2.2, 1.7)
D5-24h	18	1.1	6.6	(-1.6, 3.7)
D6-26h	21	1.2	8.3	(-1.9, 4.4)
D6-28h	19	2.0	8.7	(-1.5, 5.4)
D6-32h	19	3.6	5.9	(1.3, 6.0)
D6-36h	19	1.4	6.9	(-1.3, 4.2)
D7-48h	16	1.6	8.0	(-1.9, 5.1)

Table 19: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
CPX-351	26	22 (84.6%)	4 (15.4%)

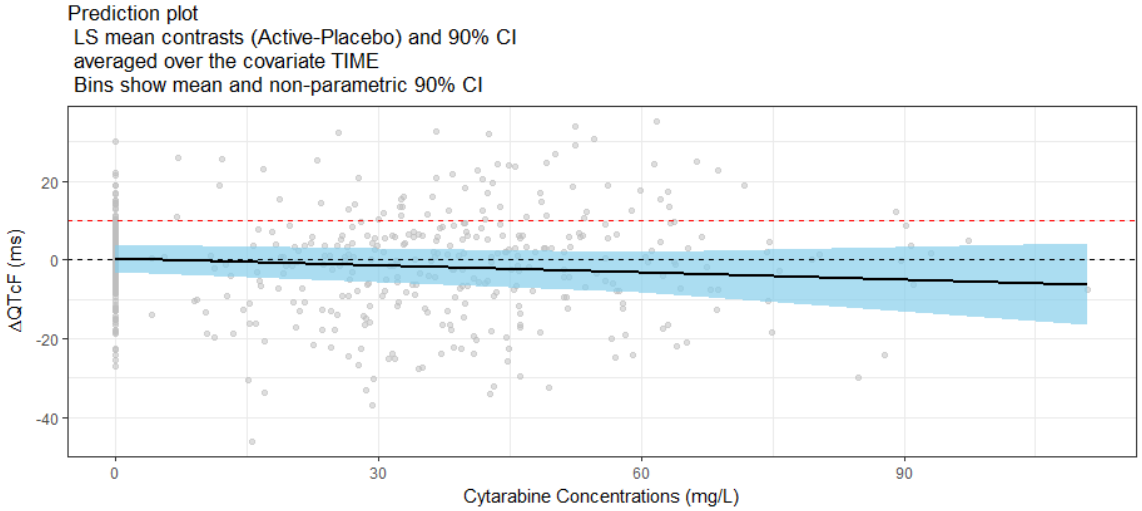
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

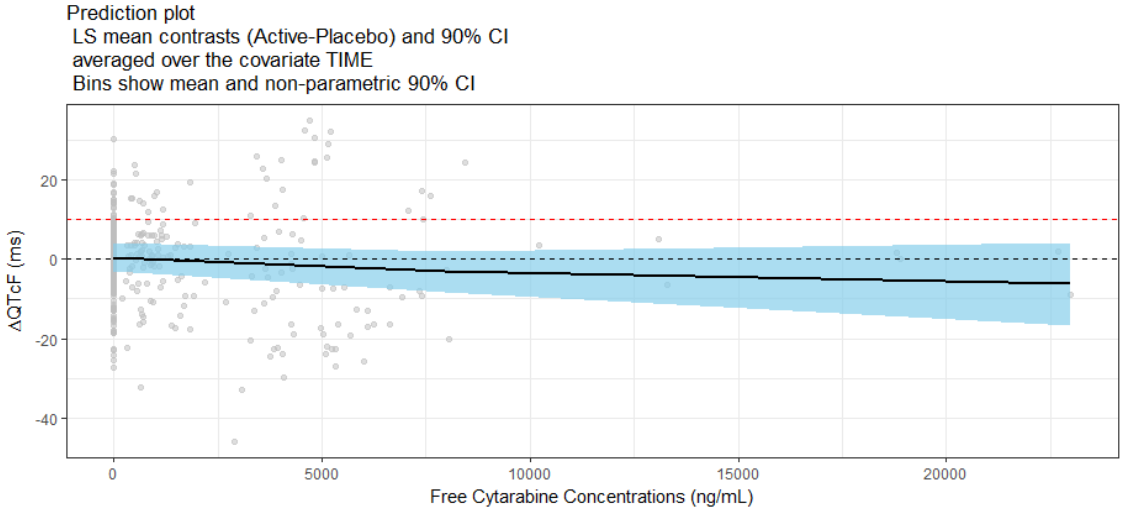
The mean drug concentration-time profile is illustrated in Section 4.2.2.4.1 above.

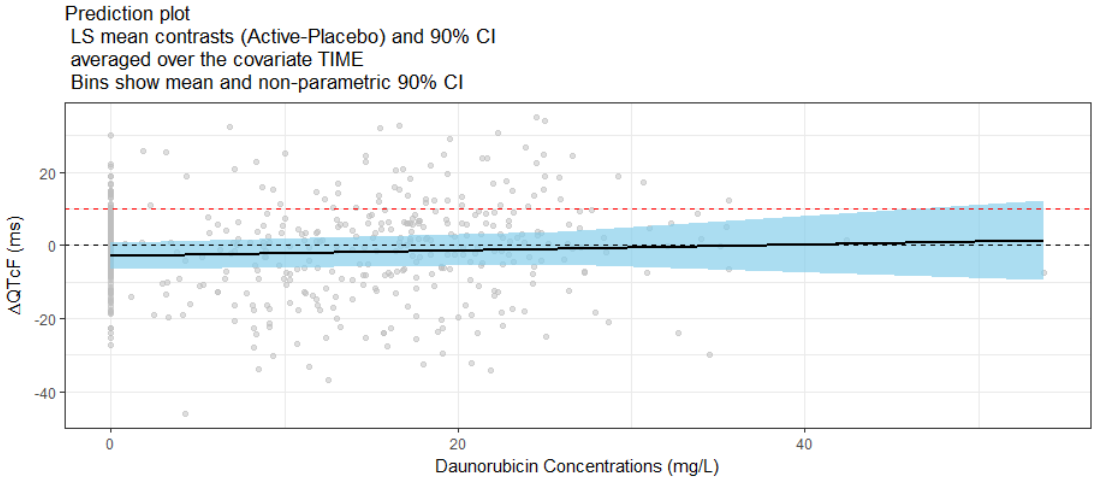
The relationship between ΔQTcF and concentrations is visualized in Figure 16. The relationships between ΔQTc and concentrations of multiple moieties were investigated separately by linear mixed-effects modeling with QTcF change from baseline (ΔQTcF) as the dependent variable. The final C-QTc model was a linear model with random effect on the intercept and slope of concentration effects. The effect of baseline QTcF and placebo effect were taken as fixed effects. There is no evident exposure-response relationship between ΔQTcF and concentrations of the moieties evaluated.

Reference ID: 4112723

Figure 16: ΔQTcF vs. Concentration of various moieties







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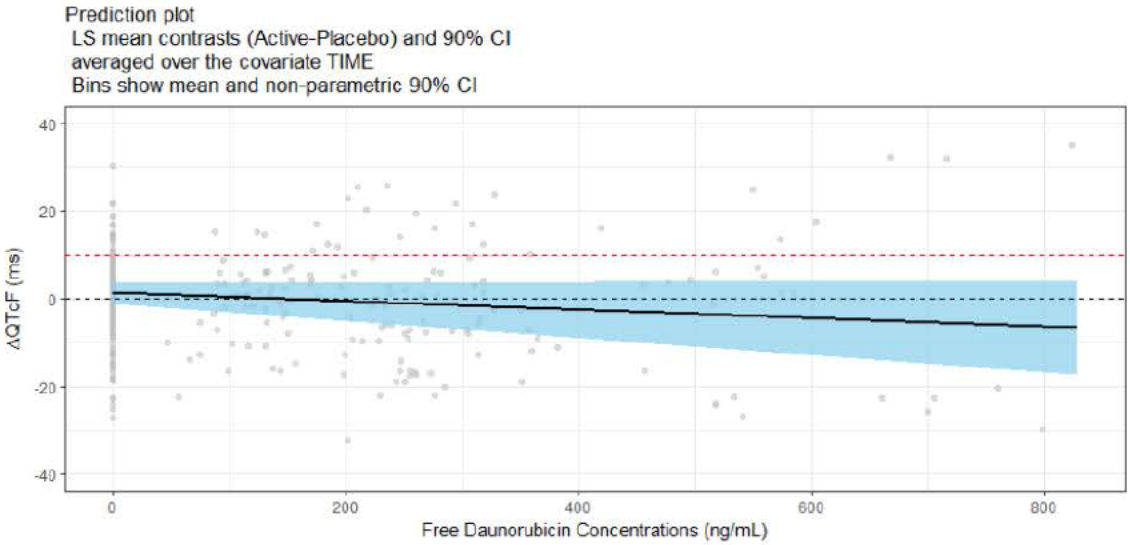
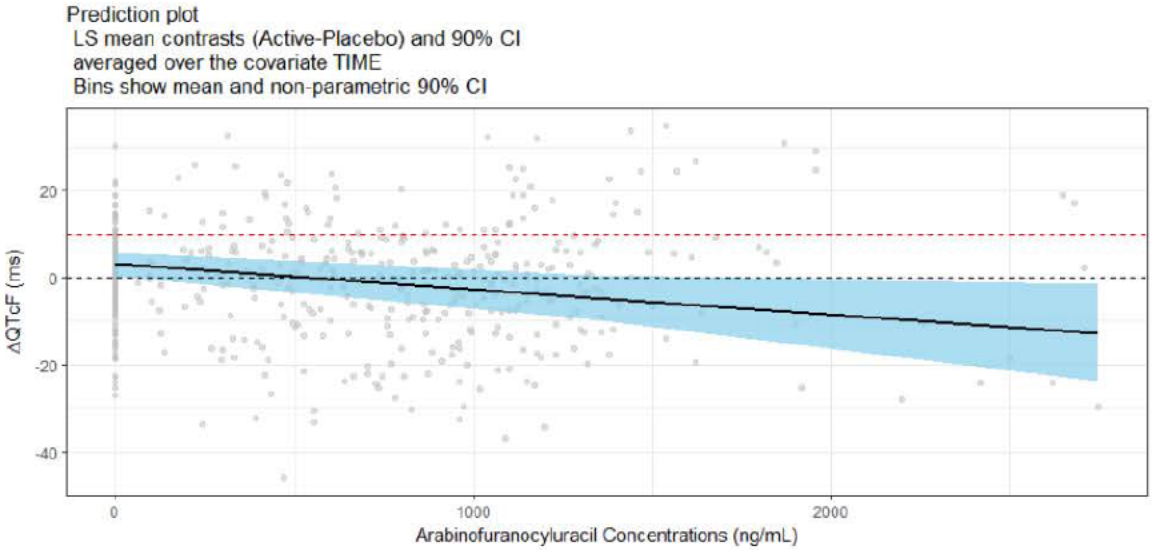
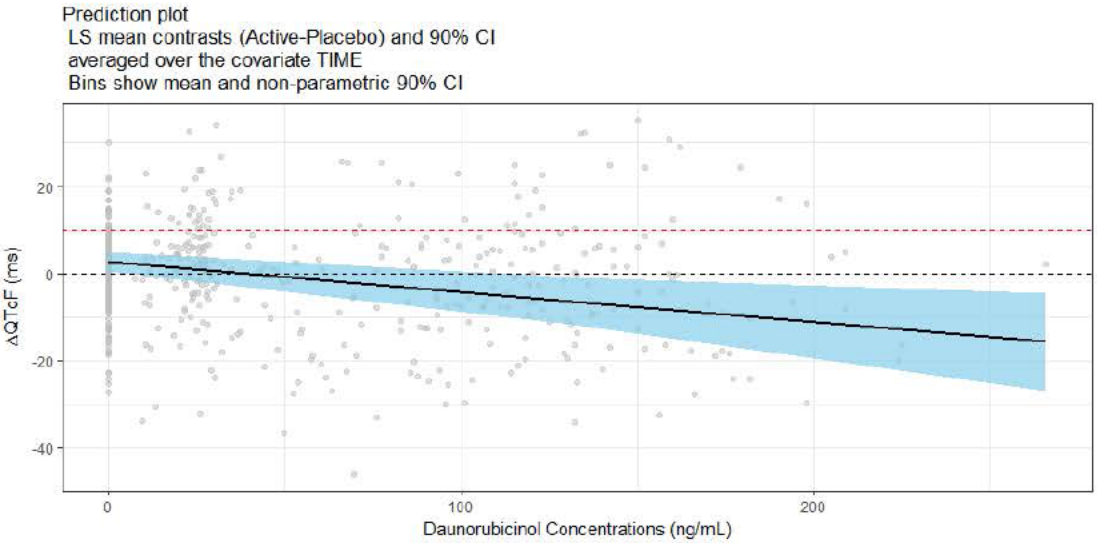






Reference ID: 4112723

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

A total of 12/26 subjects (46%) experienced cardiac AEs during the study. The most frequently reported cardiac AEs were sinus tachycardia (5/26 subjects, 19.2%) and tachycardia (4/26 subjects, 15.4%). One subject reported Grade 2 angina pectoris and atrial fibrillation. One subject reported a Grade 3 SAE of ejection fraction decreased which was considered possibly related to study drug.

None of the cardiac AEs identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Although there were no meaningful mean increases in heart rate from baseline, 16/26 (61.5%) had HR >100 bpm.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effect on PR or QRS intervals.

Reference ID: 4112723

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Cytarabine

Therapeutic dose	100 units/m^2 CPX-351 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin base) by 90 minute infusion given on days 1, 3, and 5 constitutes one induction course of therapy administered in the phase 2 studies. Up to two induction courses were to be given and up to 2 consolidation courses (same as above minus the Day 5 dose).			
Maximum tolerated dose	101 units/m^2 per day on days 1, 3 and 5			
Principal adverse events	Dose limiting adverse events: congestive heart failure, hypertensive crisis, and persistent cytopenias beyond 56 days. Most frequent adverse events: See attached table[1]. Principal adverse events appear to be related to myelosuppression and consequences. Cardiac events related to known anthracycline toxicity were and are being monitored.			
Maximum dose tested	Single Dose	Not Applicable		
	Multiple Dose	134 units/m^2 (134 mg cytarabine per m^2) given by 90 minute iv infusion on days 1, 3, 5 of first induction. Patients could receive a second induction course of the same dose and regimen or a consolidation course at the same dose on days 1 and 3. Pharmacokinetic evaluation was performed on the first induction course only.		
Exposures Achieved at Maximum Tested Dose	Single Dose (Day 1)	Dose	units/m^2	134
		N		6
		Cmax Mean (%CV)	ng/ml	62,567 (15.0)
		AUC0-48 Mean (%CV)	ng*hr/ml	1,896,454 (15.0)
	Multiple Dose (Day 5)	Dose	units/m^2	134
		N		6
		Cmax Mean (%CV)	ng/ml	89,117 (4.8)
		AUC0-inf Mean (%CV)	ng*hr/ml	5,871,447 (31.9)
Range of linear PK	Day 1: Linear, single dose pharmacokinetic characteristics from 24 – 134 units/m^2. PK data from doses below 24 units/m^2 were unreliable and not used in statistical analysis. Day 5: Linear, multiple dose pharmacokinetic characteristics from 24 – 134 units/m^2.			
Accumulation at steady state	Not Applicable			

Reference ID: 4112723

Cytarabine

Metabolites	Plasma arabinofuranosyluracil (Ara-U) was measured in this study. For conventional cytarabine, the predominant plasma metabolite is Ara-U (an inactive metabolite). Conventional cytarabine is extensively metabolized and other metabolites have been recognized. (see reference 1)			
Absorption	Absolute/Relative Bioavailability	Intravenous infusion, therefore, Not Applicable		
	Tmax Median (Day 1)	Dose	units/m^2	134
		N		6
		Tmax parent (range)	hr	1.75 (1.5 – 4.0)
		Tmax Ara-U (range)	hr	24 (8-48)
		Dose	units/m^2	101
		N		13
		Tmax parent (range)	hr	2 (1.5 – 8.0)
		Tmax Ara-U (range)	hr	24 (2-48)
Distribution	Vz mean (Day 1)	Dose	units/m^2	134
		n		6
		Vz (%CV)	mL/m^2	2,398 (9.8)
		Dose	units/m^2	101
		n		13
		Vz (%CV)	mL/m^2	2,750 (31.0)
	% bound	Not Available. Note that all parameters reported here represent "total" circulating drug levels, that is, liposome-encapsulated, protein bound and "free".		
Elimination	Route	• Not known for CPX-351. • For conventional cytarabine, 80% of radio-labeled drug is recovered in the urine within 24 hours of drug administration, primarily as Ara-U. (see reference 1) • Other routes: Not known		
	Terminal t½ Mean (Day 5)	Dose	units/m^2	134
		n		6
		t1/2 parent (%CV)	hr	46 (35.2)
		t1/2 ara-U (%CV)	hr	44.4 (33.5)

Reference ID: 4112723

Cytarabine

		Dose	units/m^2	101
		n		13
		t1/2 parent (%CV)	hr	36.9 (66.4)
		T1/2 ara-U (%CV)	hr	48.6 (43.4)
	CL Mean (Day 5)	Dose	units/m^2	134
		n		6
		CL (%CV)	ml*hr/m^2	45.9 (15.9)
		Dose	units/m^2	101
		n		13
		CL (%CV)	ml*hr/m^2	67.3 (45.5)
Intrinsic Factors* *Exploratory analysis (available on request)	Age (Day 5)	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		<60 years N	16	16
		<60 years Mean (SD)	652.9 (266.87)	30,950.5 (25,261.50)
		≥60 years N	21	21
		≥60 years Mean (SD)	669.1 (184.21)	39,380.3 (19,153.06)
	Sex (Day 5)	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		Male N	25	25
		Male Mean (SD)	640.9 (221.30)	34,153.0 (18,929.84)
		Female N	12	12
		Female Mean (SD)	706.2 (221.47)	39,030.7 (28,221.89)
	Race	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		White N	29	29
		White Mean (SD)	640.2 (209.28)	33,677.0 (18,244.94)

Reference ID: 4112723

Cytarabine

		Asian N	4	4
		Asian Mean (SD)	840.0 (312.74)	50,315.3 (37,177.71)
		Black N	2	2
		Black Mean	572.5	22,376.5
		Hispanic N	2	2
		Hispanic Mean	714.0	49,773.0
	Hepatic & Renal Impairment	Not known for CPX-351. Patients with significant abnormal renal and hepatic function are being excluded from ongoing clinical trials.		
Extrinsic Factors	Drug interactions	Not known for CPX-351. CPX-351 is a liposomal product used in serious diseases. No known drug-drug interactions in clinical data base.		
	Food Effects	Not Available		
Expected High Clinical Exposure Scenario	As CPX-351 is administered by intravenous infusion in the hospital setting, mistakes in drug administration should be rare and supra-therapeutic doses unlikely. High clinical exposures when the drug is used as intended are considered unlikely.			

Reference ID: 4112723

Daunorubicin hydrochloride

Therapeutic dose	100 units/m^2 CPX-351 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin base) by 90 minute infusion given on days 1, 3, and 5 constitutes one induction course of therapy administered in the phase 2 studies. Up to two induction courses were to be given and up to 2 consolidation courses (same as above minus the Day 5 dose).			
Maximum tolerated dose	101 units/m^2 per day on days 1, 3 and 5			
Principal adverse events	Dose limiting adverse events: congestive heart failure, hypertensive crisis, and persistent cytopenias beyond 56 days. Most frequent adverse events: See attached table[1]. Principal adverse events appear to be related to myelosuppression and consequences. Cardiac events related to known anthracycline toxicity were and are being monitored. Extravasation of liposomal anthracycline is a potential risk, but has not been observed.			
.Maximum dose tested	Single Dose	Not Applicable		
	Multiple Dose	134 units/m^2 (59 mg daunorubicin per m^2; all daunorubicn concentrations are reported as the free base) given by 90 minute iv infusion on days 1, 3, 5 of first induction. Patients could receive a second induction course of the same dose and regimen or a consolidation course at the same dose on days 1 and 2. Pharmacokinetic evaluation was performed on the first induction course only.		
Exposures Achieved at Maximum Tested Dose	Single Dose (Day 1)	Dose	units/m^2	134
		N		6
		Cmax Mean (%CV)	ng/ml	37,750 (14.5)
		AUC0-48 Mean (%CV)	ng*hr/ml	953,673 (12.7)
	Multiple Dose (Day 5)	Dose	units/m^2	134
		N		6
		Cmax Mean (%CV)	ng/ml	44,733 (5.8)
		AUC0-inf Mean (%CV)	ng*hr/ml	1,942,651 (31.9)
Range of linear PK	Day 1: Linear, single dose pharmacokinetic characteristics from 24 – 134 units/m^2. PK data from doses below 24 units/m^2 were unreliable and not used in statistical analysis. Day 5: Linear, multiple dose pharmacokinetic characteristics from 24 – 134 units/m^2.			
Accumulation at steady state	Not Applicable			

Reference ID: 4112723

Daunorubicin hydrochloride

Metabolites	Plasma daunorubicinol was measured in this study. For conventional daunorubicin, the predominant plasma metabolite is daunorubicinol (an active, antineoplastic and potentially toxic, metabolite). Conventional daunorubicin is extensively metabolized in the liver and other metabolites have been recognized. (see reference 2)			
Absorption	Absolute/Relative Bioavailability	Intravenous infusion, therefore, Not Applicable		
	Tmax Median (Day 1)	Dose	units/m^2	134
		N		6
		Tmax parent (range)	hr	2.0 (0.75-4.0)
		Tmax daunorubicinol (range)	hr	48.0 (48.0-48.0)
		Dose	units/m^2	101
		N		13
		Tmax parent (range)	hr	1.5 (1.5-8.0)
		Tmax daunorubicinol (range)	hr	48.0 (48.0-48.0)
Distribution	Vz mean (Day 1)	Dose	units/m^2	134
		n		6
		Vz (%CV)	mL/m^2	1,700 (18.2)
		Dose	units/m^2	101
		n		13
		Vz (%CV)	mL/m^2	1,997 (21.3)
	% bound	Not Available. Note that all parameters reported here represent "total" circulating drug levels, that is, liposome-encapsulated, protein bound and "free".		
Elimination	Route	• Not Known for CPX-351 • For conventional daunorubicin, 25% of the drug is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion. (see reference 2) • Other routes: Not known		
	Terminal t½ Mean (Day 5)	Dose	units/m^2	134
		n		6
		t1/2 parent (%CV)	hr	37 (31.5)
		t1/2 daunorubicinol (%CV)	hr	61.2 (59.3)
		Dose	units/m^2	101
		n		13

Reference ID: 4112723

Daunorubicin hydrochloride

		t1/2 parent (%CV)	hr	25.2 (46.1)
		t1/2 daunorubicinol (%CV)	hr	45.6 (51.1)
	CL Mean (Day 5)	Dose	units/m^2	134
		n		6
		CL (%CV)	ml*hr/m^2	50.2 (17.1)
		Dose	units/m^2	101
		n		13
		CL (%CV)	ml*hr/m^2	72.9 (31.5)
Intrinsic Factors* *Exploratory analysis (available on request)	Age (Day 5)	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		<60 years N	16	16
		<60 years Mean (SD)	684.1 (149.27)	22,990.8 (13,234.27)
		≥60 years N	21	21
		≥60 years Mean (SD)	695.5 (161.69)	27,589.2 (14,272.49)
	Sex (Day 5)	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		Male N	25	25
		Male Mean (SD)	664.5 (149.51)	24,751.1 (12,023.30)
		Female N	12	12
		Female Mean (SD)	744.9 (156.50)	27,370.8 (17,498.63)
	Race (Day 5)	parameter	Cmax/Dose	AUCinf/Dose
		Units	[(ng/ml)/(mg/m^2)]	[ng*hr/ml)/(mg/m^2)]
		White N	29	29
		White Mean (SD)	681.3 (157.49)	24,518.0 (13,564.04)
		Asian N	4	4
		Asian Mean (SD)	774.5 (143.86)	37,971.5 (10,940.08)
		Black N	2	2
		Black Mean	576.0	13,466.5
		Hispanic N	2	2
		Hispanic Mean	772.0	28,692.5
	Hepatic & Renal Impairment	Not known for CPX-351. Patients with significant abnormal renal and hepatic function are being excluded from ongoing clinical trials.		

Reference ID: 4112723

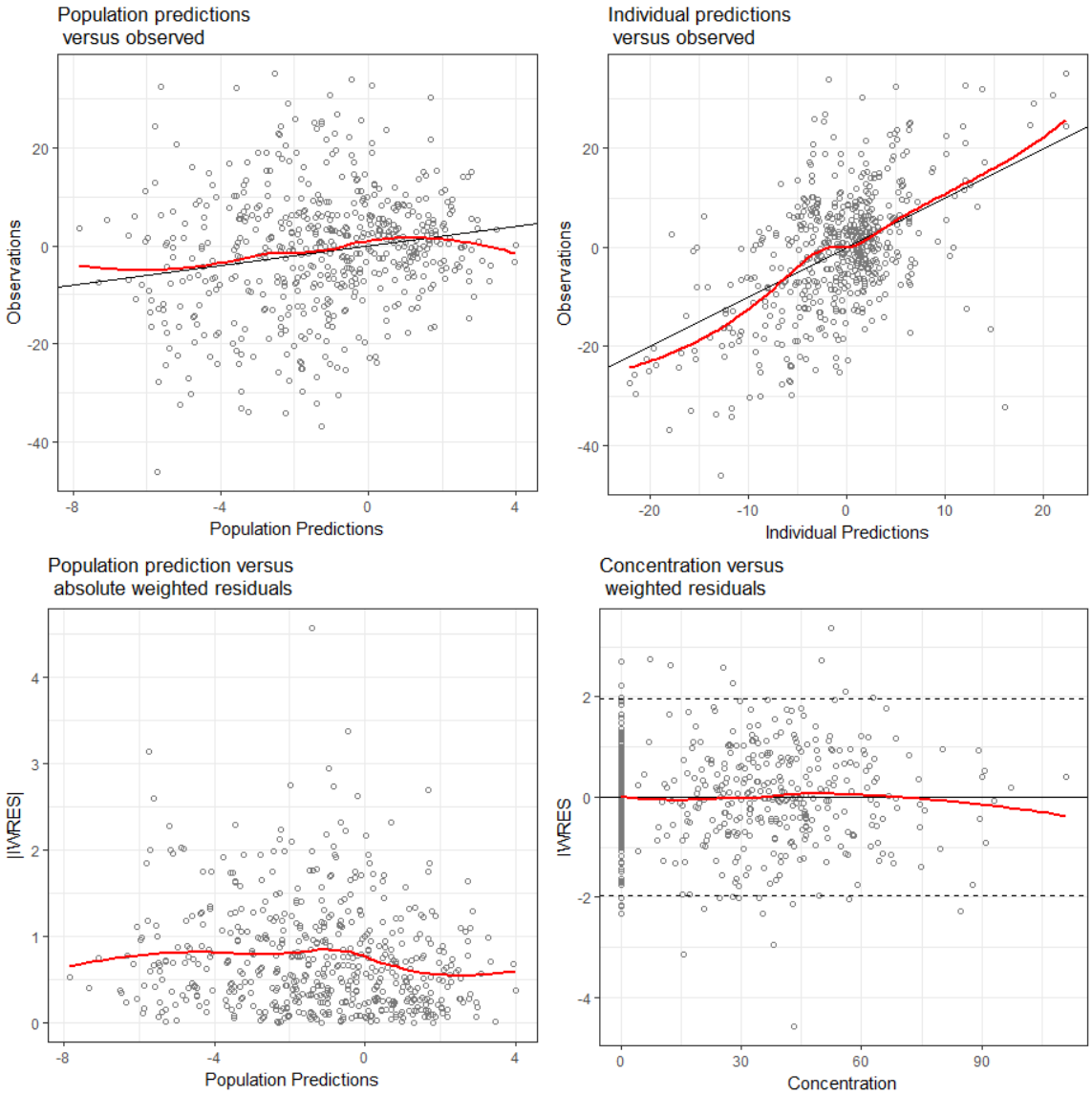
Daunorubicin hydrochloride

Extrinsic Factors	Drug interactions	Not known for CPX-351. CPX-351 is a liposomal product used in serious disease. No known drug-drug interactions in clinical data base.
	Food Effects	Not Available
Expected High Clinical Exposure Scenario	As CPX-351 is administered by intravenous infusion in the hospital setting, mistakes in drug administration should be rare and supra-therapeutic doses unlikely. High clinical exposures when the drug is used as intended are considered unlikely.	

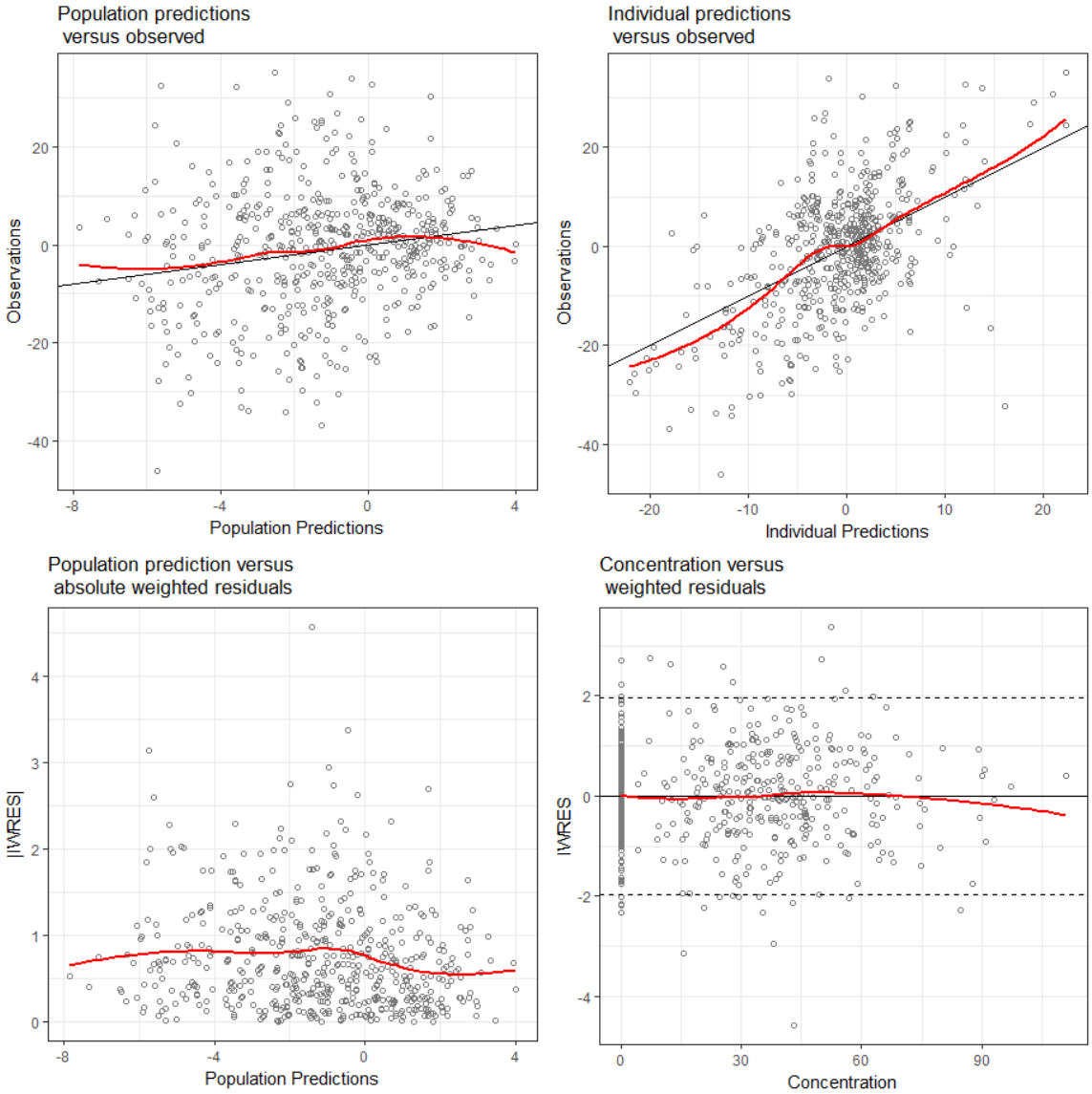
Reference ID: 4112723

6.2 EXPOSURE RESPONSE MODEL DIAGNOSIS

Cytarabine concentration vs. ΔQTcF

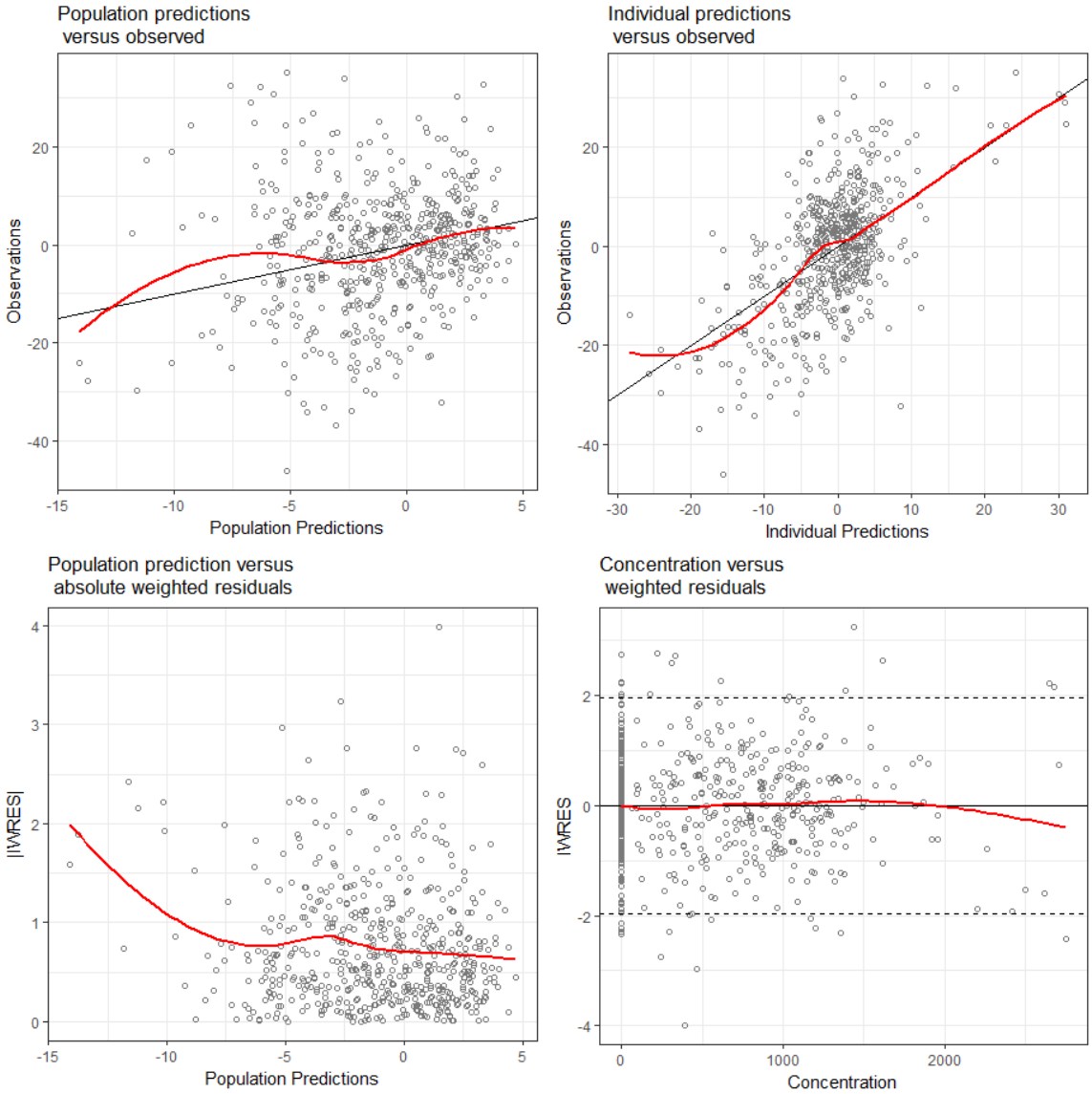


Daunorubicin concentration vs. ΔQTcF

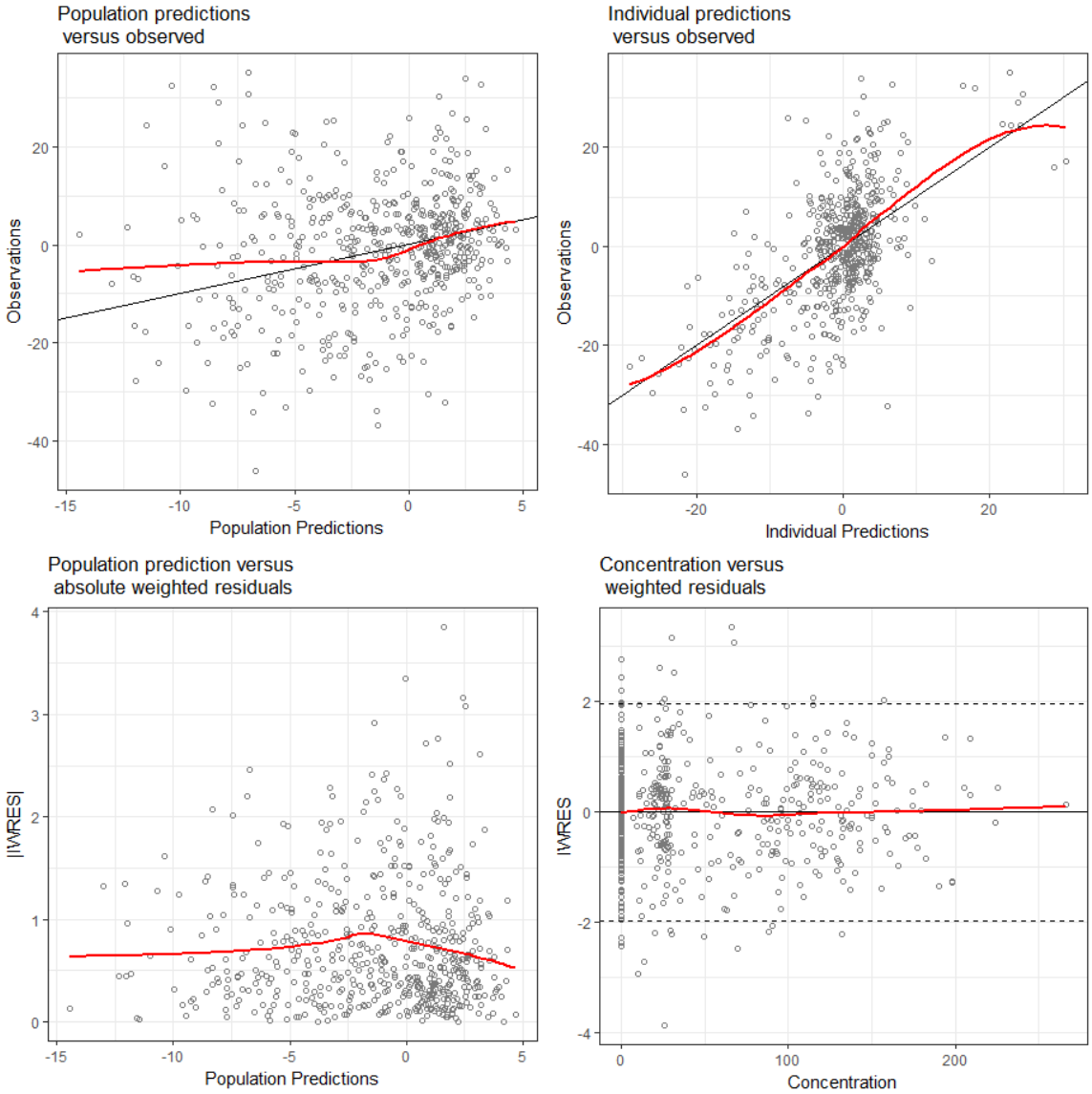


Reference ID: 4112723

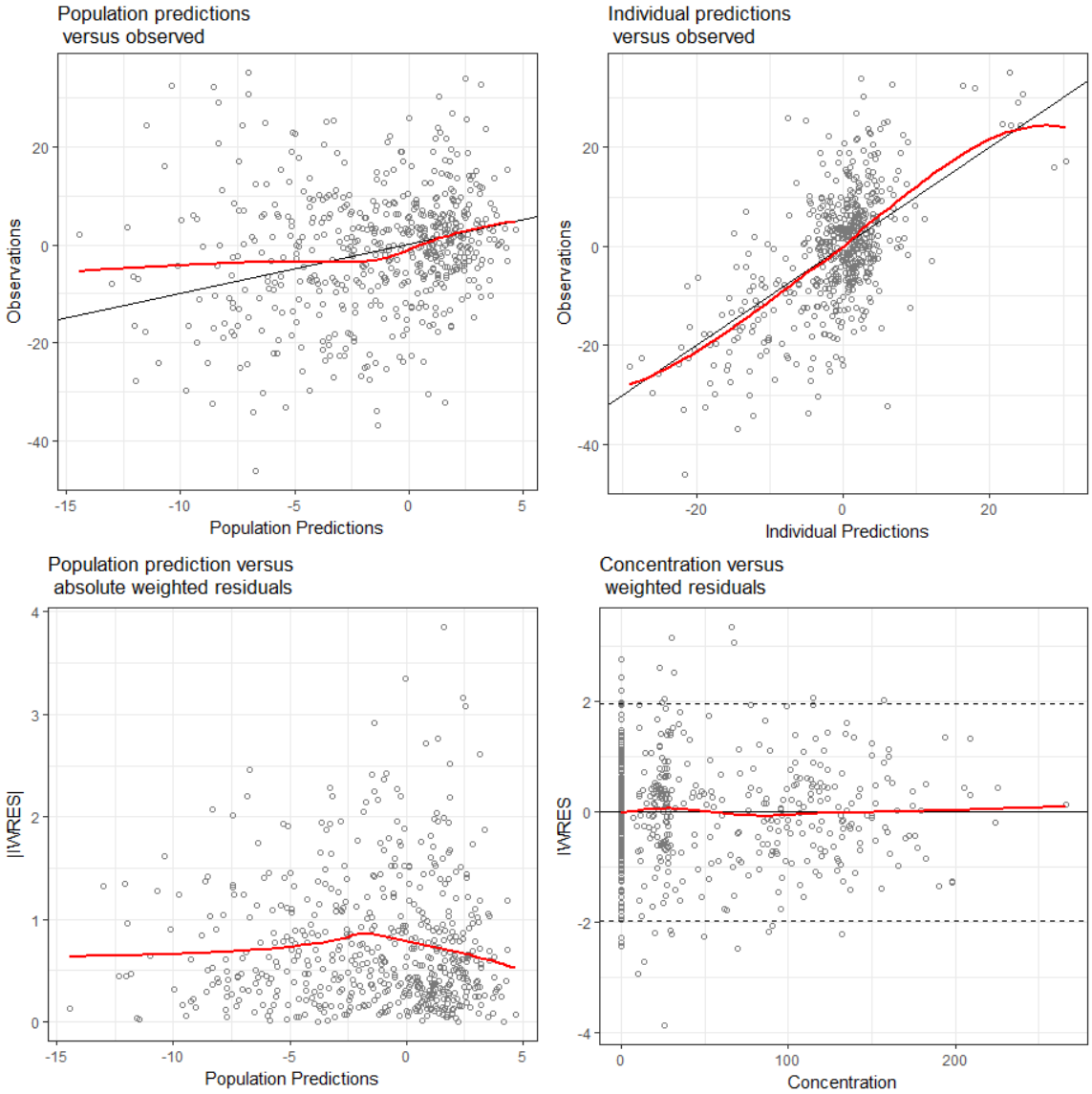
Arabinofuranocyluracil concentration vs. ΔQTcF



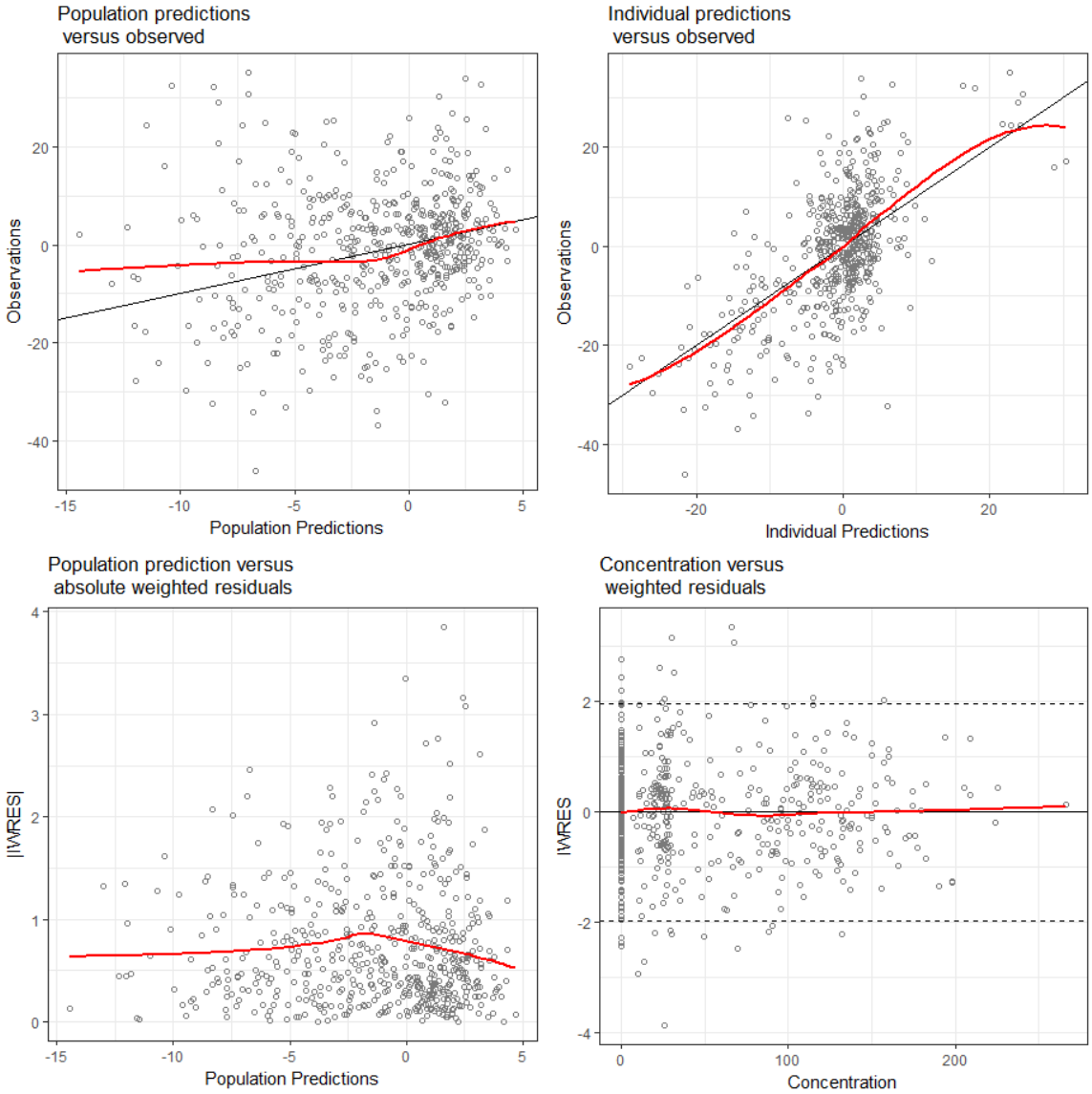
Daunorubicinol concentration vs. ΔQTcF



Free Cytarabine concentration vs. ΔQTcF



Free Daunorubicin concentration vs. ΔQTcF



Reference ID: 4112723

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/s/

LARS JOHANNESEN
06/19/2017
Chao Liu was the primary reviewer and Dhananjay Marathe was the secondary reviewer.

CHAO LIU
06/19/2017

MOH JEE NG
06/19/2017

MOHAMMAD A RAHMAN
06/19/2017

DEVI KOZELI on behalf of MICHAEL Y LI
06/23/2017
Signing for Mike as he is on leave

CHRISTINE E GARNETT
06/23/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209401

Application Type: New 505(b)(2) NDA

Drug Name(s)/Dosage Form(s): Vyxeos (cytarabine and daunorubicin) liposome for injection

Applicant: Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)

Receipt Date: March 31, 2017

Goal Date: September 30, 2017

1. Regulatory History and Applicant's Main Proposals

On March 31, 2017, Celator Pharmaceuticals, Inc. submitted the final rolling submission of NDA 209401 for CPX-351 (cytarabine and daunorubicin) liposome for injection for the treatment of adult patients with [redacted] (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). The proposed proprietary name for CPX-351 is Vyxeos.

CPX-351 was granted orphan drug designating on August 22, 2008, for the treatment of acute myeloid leukemia and on May 18, 2016, was granted breakthrough therapy designation for treatment of adults with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

Reference ID: 4104378

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Reference ID: 4104378

Selected Requirements of Prescribing Information

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Reference ID: 4104378

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015"**).

Comment:

Reference ID: 4104378

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 4104378

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

Reference ID: 4104378

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Reference ID: 4104378

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 4104378

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 4104378

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WANDA D NGUYEN
05/30/2017

PATRICIA N GARVEY
05/30/2017

THERESA A CARIOTI
05/30/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209401	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Vyxeos Established/Proper Name: CPX-351 (cytarabine and daunorubicin) liposome for Injection Dosage Form: liposome for injection Strengths: 100 mg cytarabine and 44 mg daunorubicin Route(s) of Administration: injection		
Applicant: Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company) Agent for Applicant (if applicable):		
Date of Application: March 31, 2017 Date of Receipt: March 31, 2017 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: September 30, 2017	Action Goal Date (if different): July 31, 2017	
Filing Date: May 30, 2017	Date of Filing Meeting: May 18, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of adults with h (b) (4) therapy related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2) N/A	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k) N/A	

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Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 072939	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

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Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ N/A ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

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• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		Depocyt 021041 DaunoXome 050704
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents*** *are drug products in identical dosage forms and route(s) of administration that:* ***(1)*** *contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;* ***(2)*** *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☒		Statement of no relevant patents

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Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

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Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		Form 3454, Robin Hume signature
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☒		TOC lists the 3674 in 1.1.7 but submission missing
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

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Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		Orphan designation
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan designation
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

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Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***QT-IRT 4/6/2017***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 7/29/2010 & 5/25//2011	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 5/16/2016 (pre NDA), 6/7/2016 (guidance/preNDA) , & 7/13/2016 (CMC)	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: May 18, 2017

BACKGROUND:

On March 31, 2017, Celator Pharmaceuticals, Inc. submitted the final rolling submission of NDA 209401 for CPX-351 (cytarabine and daunorubicin) liposome for injection for the treatment of adult patients with (b) (4) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). The proposed proprietary name for CPX-351 is Vyxeos.

CPX-351 was granted orphan drug designating on August 22, 2008, for the treatment of acute myeloid leukemia and on May 18, 2016, was granted breakthrough therapy designation for treatment of adults with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Wanda Nguyen	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Donna Przepiorka		Y
Division Director/Deputy	Ann Farrell Ed Kaminskas		N Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Aviva Krauss	N
	TL:	Donna Przepiorka	Y
Clinical Pharmacology	Reviewer:	Liang Li	Y
	TL:	Stacy Shord	Y
• Pharmacometrics	Reviewer:	Wentao Fu	Y
Biostatistics	Reviewer:	Xin Gao	Y
	TL:	Yuan Li Shen	Y

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Nonclinical Pharmacology/Toxicology)	Reviewer:	Michael Manning	Y
	TL:	Chris Sheth	Y
Product Quality (CMC) Review Team:	ATL:	Sherita McLamore-Hines	N
	RBPM:	Teshara Bouie	Y
• Drug Substance	Reviewer:	Katherine Windsor	Y
• Drug Product	Reviewer:	Paresma Patel	Y
• Process	Reviewer:	Kumar Janoria	N
• Microbiology	Reviewer:	David Bateman	N
• Facility	Reviewer:	Christina Capacci-Daniel	N
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
• Immunogenicity	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Anamitro Banerjee		Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Rachel Conklin	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Nicole Garrison	Y
	TL:	Hina Mehta	Y

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	N
	TL:	Janice Pohlman	N
Other reviewers/disciplines Jacqueline Jones			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to	

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demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

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Comments:	☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO

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Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☒ Not Applicable ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	☐ Not Applicable
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

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• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Richard Pazdur, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): June 19, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review

	ACTION ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

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Annual review of template by OND ADRAs completed: April 2016

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WANDA D NGUYEN
05/25/2017

PATRICIA N GARVEY
05/25/2017

THERESA A CARIOTI
05/29/2017

CLINICAL INSPECTION SUMMARY ADDENDUM

Date	May 2, 2017
From	Anthony Orencia, M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Susan D. Thompson, M.D., Team Leader, Acting GCPAB Branch Chief DCCE/OSI
To	Aviva Krauss, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Cross Discipline Team Leader Wanda Nguyen/Beatrice Kallungal, Regulatory Project Managers Division of Hematology Products
BLA	209401 (IND 072939)
Applicant	Celator Pharmaceuticals
Drug	cytarabine:daunorubicin (liposomal formulation)
NME	No
Therapeutic Classification	505b2 (breakthrough therapy drug designation)
Proposed Indication	(b) (4)
Consultation Request Date	July 6, 2016 (pre-NDA submission, rolling submission) March 31, 2017 (completed NDA rolling submission)
Summary Goal Date	September 1, 2017
Action Goal Date	September 30, 2017
PDUFA Date	September 30, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For Study CLTR0310-301, three clinical sites (Drs. Lancet, Newell, and Cortes) were selected for inspection. For Study CLTR0308-205, a single clinical site (Dr. Cortes) was selected for inspection.

The classification for the inspections of Drs. Newell and Cortes is No Action Indicated (NAI). The classification for the inspection of Dr. Lancet is Voluntary Action Indicated (VAI). The study data derived from these clinical sites are considered reliable in support of the requested indication.

2. BACKGROUND

Cytarabine is a pyrimidine analogue that affects cells predominantly during the S-phase of cell division. Incorporation of cytarabine into DNA and RNA may also contribute to its cytotoxicity. Daunorubicin is an anthracycline that exhibits anti-mitotic and cytotoxic activity via various mechanisms, including DNA-intercalation and topoisomerase II inhibition, with resultant DNA breaks.

Cytotoxicity analyses indicate that cytarabine and daunorubicin combined at a 5:1 molar ratio act synergistically in many tumor cell lines. The liposomal formulation of cytarabine and daunorubicin (CPX-351) encapsulates this fixed ratio of these agents for delivery in an attempt to optimize the synergistic molar ratio at the target. Thus, the liposomal formulation of the drug combination has been proposed to enhance therapy for use in the induction and consolidation phase in patients (b) (4) .

The data from two randomized clinical trials were submitted in support of the applicant's NDA for the treatment of adult patients with (b) (4)

CDER DHP requested inspection of three domestic clinical sites for Study CLTR0310-301. For Study CLTR0308-205, DHP requested that a single clinical site be inspected. These sites principally enrolled large numbers of study subjects and had low recorded protocol deviations, and other study risk as assessed by CDER DHP.

CPX-351 had received breakthrough therapy designation in May 2016 for the treatment of adults with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). DHP anticipated that the application would undergo an expedited priority review and requested clinical site inspections in July 2016. Study information including the protocol, case report form, sample informed consent document, and data listings from sites to be inspected were submitted by the sponsor to the IND (IND 072939) to facilitate inspection. Subsequently, the sponsor's request for a rolling submission was granted in August 2016, with submission of all modules anticipated to be complete by December 2016. Clinical site inspections continued based upon expectation of an expedited priority review and were complete by the end of September 2016.

Although nonclinical information (Module 4) was submitted to the NDA by the end of September 2016, the remaining modules were not submitted until March 31, 2017. The delay in submission of the remaining modules was attributed to: (1) data standards formatting issues of the datasets (not affecting actual data contained, (2) clinical adverse event data for studies CLTR0308-204, CLTR0308-205 and CLTR0310-301 needed revised coding and review, (3) an Active Pharmaceutical Ingredient (API) manufacturing site had received a FDA regulatory warning letter, and the alternate API supplier also had manufacturing compliance issues, and (4) a manufacturing process validation batch had out of specification results.

The filing meeting for NDA 209401 is pending.

Study Protocol CLTR0308-205

Study 205 was an open label, multicenter, randomized, parallel arm study in adult patients up to 65 years of age who received either CPX-351 or intensive salvage therapy as controls. As noted above, CPX-351 (cytarabine:daunorubicin) is a liposomal formulation of a fixed combination of the anti-neoplastic drugs, cytarabine and daunorubicin. During the induction phase treatment of AML, the following salvage therapy for the control group may be administered: (1) high dose Ara-C ± anthracycline (like daunorubicin), (2) cytarabine with daunorubicin, (3) mitoxantrone or

etoposide based regimens. During the consolidation phase, the salvage therapy for the control group followed local practice chemotherapy protocols. The primary objective of the study was to estimate the efficacy of CPX-351, at a dose of 100 units per m^2, in patients with AML in first relapse. Patients were *followed for up to one year* from the time of randomization to assess the survival at one year. The primary efficacy endpoint was the proportion of patients surviving at one year.

Study Protocol CLTR0310-301

CLTR0310-301 was an open-label, parallel arm, randomized study where patients with newly diagnosed AML including treatment-related AML (t-AML), AML in patients with a history of myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMMoL), and de novo AML in patients with specific adverse karyotypic changes (per WHO definitions) were randomized to receive either CPX-351 (Study Arm A) or cytarabine + daunorubicin (Study Arm B). The primary objective of the study was to confirm the efficacy of CPX-351 compared to "7+3" as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML associated with one of the conditions listed above [Note: "7 + 3": Cytarabine: 100- 200mg/m^2 CI x 7 days; Daunorubicin: 45 or 60mg/m^2 days 1-3 or equivalent]. The primary efficacy endpoint was overall survival. [Note: "7+3" regimen was administered intravenously with 100 mg/m^2/day of cytarabine administered by continuous infusion for 7 days and 60 mg/m^2 of daunorubicin given on days 1, 2 and 3] Patients were *followed until death or up to 5 years* following randomization. The primary efficacy study endpoint was overall survival.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Jeffrey Lancet, M.D. Moffitt Cancer Center 12902 Magnolia Drive Tampa, FL 33612	Site #002 Protocol CLTR0310-301 Subjects=23	July 27 to August 24, 2016	VAI
Laura Newell, M.D. 3181 SW Sam Jackson Park Rd, UHN73C Portland, OR 97239	Site #031 Protocol CLTR0310-301 Subjects=18	August 19 to 26, 2016	NAI

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Jorge Cortes, M.D. M.D. Anderson Cancer Center (MDACC) University of Texas 1515 Holcombe Blvd. Unit 428 Houston, TX 77030	Site #004 Protocols: CLTR0310-301 Subjects=18 and CLTR0308-205 Subjects=19	August 22 to 29, 2016	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. **Jeffrey Lancet, M.D., Study Protocol CLTR0310-301/Site #002**
   Tampa, FL

The inspection was conducted from July 27 to August 24, 2016. A total of 31subjects were screened and 23 enrolled. Of the 23 enrolled study subjects, five subjects were still in follow-up at the end of the study, and eighteen subjects died. An audit of 23 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection for failure to follow the investigational plan and inaccurate records.

(b) (4)

OSI Reviewer Comments

The above List of Inspectional Observations (483) was shared with DHP. Many of the missed LDH or uric acid assessments occurred at screening or early in the first induction cycle at a time when tumor lysis syndrome would be more common, however none of the subjects with missed assessments had renal impairment adverse events reported around that time. These protocol deviations were reported to the NDA.

Dr. Lancet responded to the regulatory violations described above in written correspondence on (b) (4) He indicated that these violations of protocol and record transcription errors were attributed to (b) (4)

He has outlined appropriate corrective measures to address these issues.

Notwithstanding the above isolated regulatory deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

2. **Laura Newell, M.D., Study Protocol CLTR0310-301/Site #031**
   Portland, OR

The inspection was conducted from August 19 to 26, 2016. A total of 19 subjects were screened, and 18 were enrolled, no subject completed the study (Note: One study subject died, seven subjects discontinued with persistent disease/lack of response to treatment, and ten study subjects were candidates for stem cell transplant). An audit of 19 screened subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

OSI Reviewer Comments:

During the study inspection, it was noted that that the sponsor did not perform or require the clinical study sites to perform a retrospective review of all AEs (specifically SAEs).

Specifically, for Dr. Newell's site, two subjects who had been classified under the initial version of the protocol as having non-serious AEs qualified to have been reported as SAEs under protocol revision 2.3; Subject #(b) (6) had neutropenic fever, and required hospitalization, and Subject #(b) (6) had "cognitive disturbance" and persistent disease.

OSI discussed the concern about apparent under-reporting of SAEs at this site with DHP. In response to an information request from DHP, the sponsor agreed to a systematic review of all adverse events reported prior to implementation of Study Protocol CLTR0310-301 version 2.3, to ensure that original protocol adverse events that were now considered to be SAEs by the amended protocol version were captured.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection. Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Jorge Cortes, M.D., Study CLTR0310-301 and CLTR0308-205/Site #004
Houston, TX

The inspection was conducted from August 22 to 29, 2016. For Study 301, a total of 21 subjects were screened and enrolled. Eighteen subjects were randomized. A total of four study subjects completed the study (eight subjects had lack of response to treatment, one subject died, and five discontinued for miscellaneous reasons). An audit of the six enrolled subjects' records was conducted.

For Study 205, 20 subjects were screened and enrolled. Nineteen subjects were randomized. Eleven subjects were on-going participants at the end of the treatment phase, six subjects had persistent disease/lack of efficacy, one subject was candidate for stem cell transplant, and one subject discontinued for other reasons. An audit of ten enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader, Good Clinical Practice Assessment Branch
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
05/02/2017

JANICE K POHLMAN
05/02/2017

SUSAN D THOMPSON
05/03/2017