CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761116Orig1s000

OTHER REVIEW(S)

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:	December 17, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761116
Product Name and Strength:	Elzonris (tagraxofusp-erzs) Injection, 1,000 mcg/mL
Applicant/Sponsor Name:	Stemline Therapeutics, Inc.
FDA Received Date:	December 6, 2018, December 11, 2018, December 14, 2018
OSE RCM #:	2018-974-02
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised prescribing information (PI), carton and container labeling for Elzonris (tagraxofusp-erzs) (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] and information request sent to the Applicant on December 12, 2018[b] recommending revisions to the strength presentation on the Carton and Container labeling.

2 CONCLUSION

The revised carton and container labeling for Elzonris (tagraxofusp-erzs) are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Ogbonna C. Revised Label and Labeling Review Memo for Elzonris (BLA 761116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 29. RCM No.: 2018-974.

[b] Kolibab, K. Email to Stemline Regulatory Affairs. Silver Spring (MD): FDA, CDER, OHOP, DHP, (US); 2018 DEC 12.

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/s/

CASMIR I OGBONNA
12/17/2018

HINA S MEHTA
12/17/2018

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

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

Memorandum

Date: 12/11/18

To: Kris Kolibab, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

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

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELZONRIS (tagraxofusp-xxxx) injection, for intravenous use

BLA: 761116

In response to DHP's consult request dated June 26, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for ELZONRIS (tagraxofusp-xxxx) injection, for intravenous use (Elzonris).

PI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on December 7, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

OPDP Does not have any comments on the PI at this time.

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/s/

RACHAEL E CONKLIN
12/11/2018

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:	November 29, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761116
Product Name and Strength:	Elzonris (tagraxofusp-erzs) Injection, 1 mg/mL
Applicant/Sponsor Name:	Stemline Therapeutics, Inc.
FDA Received Date:	November 26, 2018
OSE RCM #:	2018-974-01
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container labeling for Elzonris (tagraxofusp-erzs) (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] We had recommended Stemline include (b) (4) which they have submitted for review.

2 CONCLUSION

The revised carton and container labeling for Elzonris (tagraxofusp-erzs) are unacceptable from a medication error perspective. The strength statement and administration statement are difficult to read as currently presented. The placement of the graphic next to the proprietary name may cause confusion. Usual dosage statement on the principal display panel is duplicative. (b) (4)

[a] Ogbonna, C. Label and Labeling Review for Elzonris (BLA 761116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 20. RCM No.: 2018-974.

3 RECOMMENDATIONS FOR STEMLINE THERAPEUTICS, INC.

A. General Comments (Container Labels, (b) (4) and Carton Labeling)

1. We recommend not placing of the graphic next to the proprietary name because it can be misread or look like an additional letter in the proprietary name. Consider moving the graphic away from the proprietary name.

B. Carton Labeling

1. We recommend increasing the font size of the strength statement to ensure this important information is not overlooked.
2. We recommend increasing the font size of the "For Intravenous Infusion After Dilution" and "Single dose vial. Discard unused portion." statements as currently presented they are difficult to read.
3. We recommend removing the usual dosage statement from the principal display panel as this information is already on the back panel.

(b) (4)

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/s/

CASMIR I OGBONNA
11/29/2018

HINA S MEHTA
11/29/2018

LABEL AND LABELING 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:	November 20, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761116
Product Name and Strength:	Elzonris (tagraxofusp-xxxx) Injection, 1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Stemline Therapeutics, Inc.
FDA Received Date:	June 21, 2018, October 23, 2018, and November 8, 2018
OSE RCM #:	2018-974
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Hematology Products (DHP) to review the Prescribing Information (PI), carton labeling, and container labels for Elzonris (tagraxofusp-xxxx) injection for areas of vulnerability that may lead to medication errors. On June 21, 2018, Stemline Therapeutics, Inc. submitted final part 3 of a rolling submission for original BLA 761116 for Elzonris (tagraxofusp-xxxx) injection, a targeted therapy directed to CD123 indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN)

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	F – N/A
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

DMEPA evaluated the proposed Prescribing Information (PI), carton and container labeling for areas of vulnerability in regards to medication error. We note the use of the terminology [redacted] (b) (4) " throughout labeling. We defer to the Office of Pharmaceutical Quality for the appropriateness of packaging type term.

We note the complexity of the dilution and administration instructions presented in the PI. Specifically, we note the 2-step preparation process of Elzonris and the administration process of using a Y-connector described in the PI may be difficult to do by healthcare professionals in real-world settings. We sent an email to the Clinical team on October 17, 2018 to determine how the product was prepared in the clinical trials. In their response the clinical team stated it was prepared by the pharmacy and the submission did not contain the pharmacy manual. Clinical Review Team sent an Information Request (IR) to Applicant on October 30, 2017 for the pharmacy manual. Stemline submitted the pharmacy manual on October 23, 2018. According to the manual the preparation involves the need of an empty 10 mL vial for preparation. On

November 1, 2018 Stemline responded to the Agency IR regarding availability of an empty 10 mL vial in pharmacies, sterility concerns of the need to enter the 'empty' vial 3 times, (b) (4) In their response, Stemline, stated they assessed the availability of ancillary supplies (including 10 mL empty vials) and determined the required components are readily available as stock items by pharmacies. The response stated educational materials for preparation and administration will be provided that will specify the use of a new syringe for each three separate entries into the 10 mL vial to mitigate sterility concerns. Stemline stated the Y-connector infusion was determined to be the preferred method of administration as it allows for a very rapid transition from the product supply to the flush stage of delivery without excessive manipulation and enables use of the syringe pump for a controlled and consistent rate of delivery throughout dose administration.

In an email response from Office of Pharmaceutical Quality (OPQ) dated November 6, 2018 to assess if entering the empty vial 'three times' would raise sterility concerns and whether this would be mitigated by the applicant's proposal to use "a new syringe for each of the three separate entries into the 10 mL vial" OPQ recommended that the PI should state a "sterile" vial should be used.

On November 5, 2018 we sent an IR to the Applicant recommending that the required components/supplies and detailed steps to prepare, instructions for dose administration set-up, and delivery of Elzonris be included in the PI. We note the Applicant implemented our recommendations into the PI on November 8, 2018.

We identified other areas of concern in the PI in addition to the carton and container labeling that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information
    a. Dangerous abbreviations, symbols, and dose designations are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve

such error prone abbreviations in the approved labeling of products. Revise all instances of "μg" to "mcg" where dosing is described to prevent confusion.

B. Highlights, Dosage and Administration
    a. We recommend dosing information to be the first bullet and combining it with the information from the second bullet. Revise to [redacted] 12 mcg/kg [redacted] over 15 minutes once daily on days 1 through 5 of a 21 day cycle. [redacted] (2.1)"
    b. Consider adding a bullet stating additional important preparation and administration information is in full prescribing information. Add "See full prescribing information for instructions on preparation and administration of drug. (2.4, 2.5)"

C. Full Prescribing Information, Section 2.2 Preparation for Administration
    a. Second bullet should contain information regarding the time required for thawing of drug. Revise the information in the bullet for clarity and define the room temperature the thawed vials can be held at.

4.2 RECOMMENDATIONS FOR STEMLINE THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this BLA 761116:

1. Container Labels
    a. To improve readability we recommend revising the font of the strength statement.
    b. We recommend revising [redacted]
    c. We recommend removing [redacted]
    d. Consider revising the statement [redacted] to read "Single-Dose Vial – Discard Unused Portion" [redacted]
    e. The drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual vial as required per 21CFR 201.25(c)(2).
    f. Revise the route of administration statement to read as follows: For Intravenous Infusion After Dilution.
    g. If space permits, consider adding the NDC number to avoid confusion.
    h. Name of manufacturer or distributor of the drug is required on container labels. We recommend adding this information per 21 CFR 201.10(i).
    i. We recommend revising the format of the expiration date as currently presented. We recommend that the human-readable expiration date on the drug package label

include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. Carton Labeling
   a. See 1.b through 1.f.
   b. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
      [1] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
   c. Relocate the strength out of the green background to appear underneath the dosage form to improve readability.
   d. Consider debolding the "Rx Only" statement to increase the prominence of other critical information on the label.
   e. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
   f. In the Ingredients section, the statement "Each (b) (4) contains (b) (4) tagraxofusp, 50.0 mg of sorbitol…"contains trailing zeros. We recommend removing the trailing zeros to avoid a ten-fold misinterpretation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elzonris (tagraxofusp-xxxx) received on June 21, 2018, from Stemline Therapeutics, Inc.

Table 2. Relevant Product Information for Elzonris (tagraxofusp)	
Initial Approval Date	N/A
Active Ingredient	Tagraxofusp-xxxx
Indication	Elzonris is a targeted therapy directed to CD123 indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1 mg/mL
Dose and Frequency	• Premedicate with an H1-histamine antagonist, acetaminophen, corticosteroid and H2-histamine antagonist prior to each ELZONRIS infusion. • (b) (4) • Administer ELZONRIS at 12 mcg/kg/day over 15 minutes once daily on days 1-5 of a 21 day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. • Administer the first cycle of ELZONRIS in the inpatient setting. Subsequent cycles may be administered in the inpatient or appropriate outpatient setting
How Supplied	ELZONRIS is supplied as a (b) (4), sterile, (b) (4) glass vials (b) (4) NDC 72187-0401-1
Storage	(b) (4) Protect ELZONRIS from light by storing in the original package until time of use. Vials should be thawed prior to preparation
Container Closure	2 mL glass vials

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 5, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Elzonris. Our search identified no previous reviews.

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,[a] along with postmarket medication error data, we reviewed the following Elzonris labels and labeling submitted by Stemline Therapeutics, Inc.

- Container label received on June 21, 2018
- Carton labeling received on June 21, 2018
- Prescribing Information (Image not shown) received on June 21, 2018 \\cdsesub1\evsprod\bla761116\0004\m1\us\114-label\1141-draft-label\proposed.docx
- Prescribing Information (Image not shown) received on November 8, 2018 \\cdsesub1\evsprod\bla761116\0026\m1\us\114-label\1141-draft-label\proposed.docx

G.2 Label and Labeling Images

a. Container Label for Elzonris 1 mg/mL injection:

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

a. Carton Label for Elzonris 1 mg/mL injection:

(b) (4)

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/s/

CASMIR I OGBONNA
11/20/2018

HINA S MEHTA
11/21/2018

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

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)

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Date of This Review:	November 9, 2018
Responsible OND Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761116
Product Name and Strength:	Elzonris (tagraxofusp-erzs) Injection 1 mg/mL
Product Type:	Single Ingredient Product
Applicant/Sponsor Name:	Stemline Therapeutics, Inc. (Stemline)
FDA Received Date:	June 21, 2018
OSE RCM #:	2018-1321
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Stemline for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761116.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On June 21, 2018, Stemline submitted a list of 10 suffixes, in their order of preference, to be used in the nonproprietary name of their product[a]. Table 1 presents a list of suffixes submitted by Stemline:

Table 1. Suffixes submitted by Stemline***	
1.	erzs
2.	(b) (4)
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

We reviewed Stemline's proposed suffixes in order of preference listed by Stemline, using the principles described in the applicable guidance.[b]

2.1 tagraxofusp-erzs

Stemline's first proposed suffix, -erzs, is comprised of four distinct letters. We note that the letters 'er' in the suffix represent the medical abbreviation for 'extended-release'. We considered whether the inclusion of the letters 'er' within the suffix could be misleading or a source of confusion and errors, but we could not identify a plausible risk based on the expected use of this product or based upon known causes of medication errors.

We determined that the proposed suffix -erzs, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be

[a] Proprietary Names-Tagraxofusp Suffix for BLA 761116. New York (NY): Stemline Therapeutics, Inc.; 2018 JUN 21. Available from: \\cdsesub1\evsprod\bla761116\0004\m1\us\118-prop-names\prop-names.pdf

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. Per an email correspondence dated November 5, 2018, OPDP did not identify any concerns that would render this proposed suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on November 9, 2018.

4 CONCLUSION

We find Stemline's proposed suffix -erzs acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to tagraxofusp-erzs.

4.1 Recommendations for Stemline Therapeutics, Inc.

We find the nonproprietary name, tagraxofusp-erzs, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, tagraxofusp-erzs will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

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/s/

CARLOS M MENA-GRILLASCA
11/09/2018

DANIELLE M HARRIS
11/14/2018

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	**BLA 761116**
Application Type	**NME**
Proprietary Name **(nonproprietary name)**	**Elzonris** **(tagraxofusp-xxxx) [suffix not finalized]**
Receipt Date	**06/21/18**
PDUFA Goal Date **(Internal Goal Date)**	**02/21/19**
Review Classification	**Expedited review**
Proposed Indication	**ELZONRIS is a CD123-directed cytotoxin for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)**
Dosing Regimen	**12µg/kg/day over 15 minutes once daily on days 1-5 of a 21 day cycle.**
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application:

Stemline Therapeutics has submitted a BLA for ELZONRIS for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Documents Reviewed: SD4

Module 1.1 Cover Letter

Module 1.14.Labeling, 1.14.1.2 Annotated Draft Labeling Text, 1.14.1.3 Draft Labeling Text

In this review, I propose labeling recommendations and edits in the Elzonris labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Elzonris.

The following pages contain the working version of the Elzonris labeling with my recommended edits and comments (identified as 'KV1' through 'KV42'). Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Elzonris labeling.

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/s/

VIRGINIA E KWITKOWSKI
09/12/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	761116
Brand Name	ELZONRIS
Generic Name	Tagraxofusp, SL-401
Sponsor	Stemline Therapeutics, Inc
Indication	Treatment of patients with blastic plasmacytoid dendritic cell neoplasm
Dosage Form	Injection for intravenous (IV) infusion
Drug Class	CD123-directed cytotoxin
Therapeutic Dosing Regimen	12 μg/kg/day x 5 days every 21 days
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	12 μg/kg/day x 5 days every 21 days
Submission Number and Date	004 / 6/21/2018
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

The effect of tagraxofusp was evaluated in a 4-stage, non-randomized, open-label dose escalation and expansion, multi-center study. No large QTc prolongation effect (i.e., > 20 ms) of tagraxofusp (12 μg/kg/day x 5 days every 21 days) was observed, consistent with tagraxofusp being a large protein and therefore having a low likelihood of direct ion channel interaction. The clinical data do not suggest any off-target effects for QTc prolongation.

Consistent with other product labels for monoclonal antibodies and targeted large therapeutic proteins, the QT-IRT is proposing not to include this statement in the label. As a large protein, tagraxofusp has low likelihood of direct ion channel interactions and the QT-IRT doesn't recommend concentration-QTc analysis for these products. We defer final labeling decisions to the Division.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Tagraxofusp is a 524-amino acid, recombinant fusion protein in which the native receptor-binding domain of diphtheria toxin (DT) has been replaced with human interleukin-3 (IL-3). The tagraxofusp protein consists of an N-terminal methionine, followed by the first 388 amino acids of DT comprising the catalytic and translocation domains. The DT fragment (Q388R variant) is genetically fused at the C-terminus through a His-Met dipeptide linker to the N-terminus of the full 133-amino acid sequence of human IL-3. The IL-3 domain targets tagraxofusp to cells that express the IL-3R. Upon binding to the IL-3R, tagraxofusp is internalized by receptor-mediated endocytosis into early endosomes and lysosomes. The catalytic domain of DT then translocates through the vesicle membrane and is released from the tagraxofusp molecule in the cytosol, where it inactivates elongation factor 2 through adenosine diphosphate ribosylation, leading to irreversible inhibition of protein synthesis and subsequent induction of cellular apoptosis.

Tagraxofusp is intended for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). The maximum proposed therapeutic dosing of Tagraxofusp is 12 μg/kg/day administered as a daily IV infusion (15 min infusion) for up to 5 consecutive days of a 21-day cycle, for multiple cycles.

Reviewer's comments: Tagraxofusp is a large protein with 524-amino acids. The DT and IL-3 fragments have large molecular weight and they are released from tagraxofusp in the cytosol. No small fragments are expected to disassociate in systemic circulation. Therefore, tagraxofusp is expected to have a low likelihood of direct ion channel interaction (ICH E14 Q&A (R3) 6.3).

2.2 MARKET APPROVAL STATUS

Tagraxofusp is not approved for marketing in any country.

2.3 PRECLINICAL INFORMATION

Refer to Highlights of Clinical Pharmacology and Cardiac Safety table in previous QT-IRT review under IND 114513 dated 09/20/2017 in DARRTS.

2.4 CLINICAL CARDIAC SAFETY EXPERIENCE

Refer to Highlights of Clinical Pharmacology and Cardiac Safety table in previous QT-IRT review under IND 114513 dated 09/20/2017 in DARRTS.

Additional information was provided in Section 4.2 of the ISS in the BPDCN Module 5.3.5.3:

No trend was apparent over time or among patient populations with regard to change from baseline in ECG parameters through C6 (ISS, Table 1.8.1.1).

In total, 6 (5%) patients had electrocardiogram QT prolonged reported as a TEAE (ISS, Table 1.4.2.1), all of whom received tagraxofusp 12 μg/kg/day. For 2 patients, this event was assessed as Grade 3 in intensity and as Grade 1 or 2 in intensity for the remaining 4

patients. No cases were considered serious or led to treatment discontinuation. None of these 6 patients experienced syncope or pre-syncope.

Overall, 46 (37%) of 125 patients had a cardiac disorder reported as a TEAE (ISS, Table 1.4.2.1). Cardiac disorders reported for >2 patients overall were tachycardia (21 patients; 17%), sinus tachycardia (12 patients; 10%), atrial fibrillation (4 patients; 3%), and bradycardia, palpitations, pericardial effusion, and sinus bradycardia (each 3 patients; 3%). Most cardiac disorders were assessed as unrelated to tagraxofusp. Twelve (10%) patients experienced a tagraxofusp-related cardiac disorder, most commonly tachycardia (6 patients; 5%) and sinus tachycardia (4 patients; 3% (ISS, Table 1.4.5.1). A cardiac disorder was serious for 7 (6%) patients, with no particular such event reported for >1 patient (ISS, Table 1.4.6.1). A serious cardiac disorder was considered tagraxofusp-related for 2 patients, including 1 case each of ventricular fibrillation (Study 0114, Patient (b) (6)) and pericardial effusion (Study 0314, Patient (b) (6)). These findings suggest no direct QT prolongation effect as a result of tagraxofusp treatment and no specific serious cardiac toxicity attributable to tagraxofusp.

2.5 CLINICAL PHARMACOLOGY

Refer to Highlights of Clinical Pharmacology and Cardiac Safety table in previous QT-IRT review under IND 114513 dated 09/20/2017 in DARRTS.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 114513 *(see the QT-IRT memo dated 09/20/2017)*. The proposed analysis and reporting plan were concluded as reasonable.

The sponsor submitted the CSR for study STML-401-0114 and a separate concentration-QTc report (SFM0103F), electronic datasets, and waveforms to the ECG warehouse.

3.2 STUDY WITH ECG DATA

3.2.1 Title

SL-401 in patients with acute myeloid leukemia or blastic plasmacytoid dendritic cell neoplasm

3.2.2 Protocol Number

STML-401-0114

3.2.3 Study Dates

Study period: March 17, 2017 – May 7, 2017

3.2.4 QT Objectives

- To evaluate the relationship between tagraxofusp concentrations and duration of the Fridericia-corrected QT interval (QTcF)

- To evaluate the relationship between tagraxofusp concentrations and the duration of the RR interval
- To evaluate, if the data sufficiently allow, whether tagraxofusp neutralizing antibodies (SL-401 NAb) alter the relationships between tagraxofusp concentration and electrocardiogram (ECG) metrics, if one exists

3.2.5 Study Description

3.2.5.1 Design

This is a 4-stage, non-randomized, open-label, dose escalation and expansion, multi-center study in patients with acute myeloid leukemia (AML) or BPDCN. In Stage 1, cohorts of 3-6 patients were treated with doses of tagraxofusp at 7, 9, 12, or 16 µg/kg/day for 5 consecutive days every 21 days. Stages 2-4 are safety expansion and efficacy assessment stages with patients receiving treatment at the maximum tolerated or tested dose from Stage 1.

3.2.5.2 Controls

This is a single-arm study.

3.2.5.3 Blinding

The treatment group was not blinded.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

Tagraxofusp was administered by 15-minute intravenous infusion daily for 5 days followed by 16 drug-free days, for a cycle length of 21 days.

- Stage 1: tagraxofusp liquid dosage form at dose levels of 7 (n=6), 9 (n=3), 12 (n=8), and 16 (n=6) µg/kg/day in patients with BPDCN and AML. The 16 µg/kg/day dose will be evaluated only in patients with AML.
- Stage 2 (n=58): 12 µg/kg/day; liquid dosage form in all BPDCN patients (n=13 as first line treatment and n=10 for relapsed/refractory BPDCN) and most AML patients; (b) (4) dosage form in a subset of AML patients.
- Stage 3 (n=13): 12 µg/kg/day liquid dosage form as first-line treatment for patients with BPDCN.
- Stage 4 (n=2, ongoing): tagraxofusp (b) (4) dosage form at 12 µg/kg/day for treatment of first-line and R/R BPDCN patients.

3.2.6.2 Sponsor's Justification for Doses

Not provided.

Reviewer's Comment: No accumulation is expected with multiple dosing. Tagraxofusp, as a therapeutic protein, is not expected to have an increase in exposure due to intrinsic or extrinsic factors. The study doses are adequate to cover clinical relevant exposure at the therapeutic dose to rule out large effect (i.e. 20 ms).

3.2.6.3 Instructions with Regard to Meals

Not applicable.

Reviewer's Comment: Food effect is not expected for this injectable product for IV infusion.

3.2.6.4 ECG and PK Assessments

All patients had a 12-lead ECG performed at the Screening visit, pretreatment visit, pre-infusion on Day 1-5 (Up to Day 10 if Infusion[s] Held), as well as Day 21 (and Day 28 only if delayed end of cycle) of each cycle. During the days when patients underwent PK sampling, time-matched measurements of tagraxofusp concentration and ECG data were collected at pre-infusion, 0.5, and 1 hour post-infusion on Day 1 (Infusion 1) and Day 5 (Infusion 5) of Cycles 1 and 3.

Reviewer's Comment: PK/ECG sampling should be adequate to capture effect near Tmax (end of infusion). ECG sampling should be adequate to evaluate potential delayed effect at 24-hour post-dose.

3.2.6.5 Baseline

Baseline is defined as the pre-infusion QTcF measurement on Day 1 of Cycle 1 (Cycle 1 Infusion 1).

3.2.7 ECG Collection

Standard 12- Lead ECGs were obtained.

Reviewer's comment: Overall ECG acquisition and interpretation in this study appears acceptable.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

A total of 95 subjects enrolled; 7 mcg/kg/day (n=6), 9 mcg/kg/day (n=3), 12 mcg/kg/day (n=80) and 16 mcg/kg/day (n=6).

3.2.8.2 Statistical Analyses

3.2.8.2.1 Categorical Analyses

Table 1 presented the sponsor's categorical analysis of PR, QRS, and QTcF by disease.

Table 1: Sponsor's Categorical Summay of PR, QRS and QTcF by (Safety Population)

Visit [1]	Parameter	Statistic	BPDCN Patients (N=47)	AML Patients (N=49)
Baseline	Received at least one dose of SL-401	N	46	49
	QTcF > 450 msec	N (%)	6 (13.0)	6 (12.2)
	QTcF > 480 msec	N (%)	0	0
	QTcF > 500 msec	N (%)	0	0
	PR > 200 msec	N (%)	6 (13.0)	2 (4.1)
	QRS > 100 msec	N (%)	22 (47.8)	9 (18.4)
At Any Time	Received at least one dose of SL-401	N	46	49
	QTcF > 450 msec	N (%)	12 (26.1)	14 (28.6)
	QTcF > 480 msec	N (%)	4 (8.7)	2 (4.1)
	QTcF > 500 msec	N (%)	3 (6.5)	0
	QTcF Increase > 30 msec	N (%)	11 (23.9)	8 (16.3)
	QTcF Increase > 60 msec	N (%)	2 (4.3)	0
	PR > 200 msec and > 25% increase	N (%)	2 (4.3)	2 (4.1)
	QRS > 100 msec and > 25% increase	N (%)	3 (6.5)	7 (14.3)

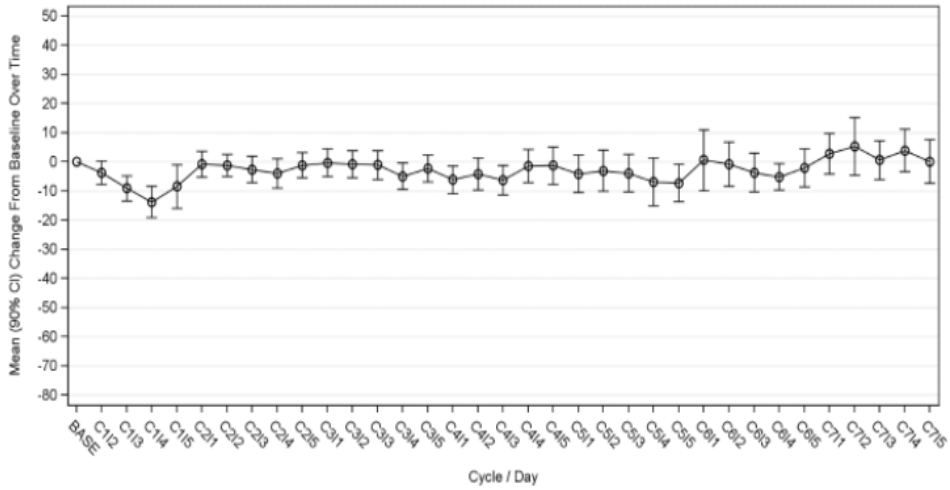
Source: Study report STML-401-0114, Table 14.3.4.11A

Reviewer's Comments: The FDA reviewer checked the data and got similar results.

3.2.8.2.2 Central Tendency

Figure 1 presented the sponsor's descriptive statistics for QTcF over time for all patients in safety population.

Figure 1: Sponsor's Descriptive Statistics for QTcF over Time for all Patients (Safety Population)



Abbreviations: BASE = Pre-infusion Timepoints; C = Cycle; CI = Confidence Interval; D = Day; I = Infusion; QTcF = Fridericia-corrected QT Interval

Source: Study report STML-401-0114, Figure 12-16

Reviewer's Comments: The FDA reviewer checked the data and got similar results. In addition, no clinically relevant effects on PR or QRS intervals were detected.

3.2.8.3 Safety Analysis

Five (5%) patients had ECG QT prolonged reported as a TEAE, including 3 BPDCN patients (6%) and 2 AML patients (4%), all of whom received SL-401 at 12 μg/kg/day. All 3 BPDCN patients had at least 1 QTcF interval >500 ms. None of these 5 patients experienced syncope or presyncope or had a cardiac TEAE. No cases were considered serious or led to treatment discontinuation.

No patient experienced Torsade de pointes during the study.

Among all 96 patients, 3 (3%) had a clinically significant abnormal ECG finding at any time on study, including 2 BPDCN patients (4%) and 1 AML patient (2%), as follows.

- Patient (b) (6) (first-Line BPDCN) had ECG evidence of sinus tachycardia pre-infusion at C1Inf5.
- Patient (b) (6) (R/R BPDCN) had ECG evidence of sinus tachycardia with supraventricular premature complexes and left axis deviation at C1Inf3.
- Patient (b) (6) (AML), had ECG evidence of sinus tachycardia at C1Inf2 that was related to PD.

Overall, 37 (39%) of 96 patients had a cardiac disorder reported as a TEAE, with the incidence of such events being 34% (16/47) and 43% (21/49) in BPDCN patients and AML patients, respectively. Most individual cardiac disorders were reported in 1 or 2 patients only. Cardiac disorders reported for >2 patients overall were tachycardia (17 patients; 18%), sinus tachycardia (8 patients; 8%), atrial fibrillation (4 patients; 4%), and bradycardia and sinus bradycardia (each 3 patients; 3%).

3.2.8.4 Clinical Pharmacology

3.2.8.4.1 Pharmacokinetic Analysis

The sponsor did not provide summary statistics on SL-401 exposure.

3.2.8.4.2 Exposure-Response Analysis

The sponsor performed exposure-response analysis between tagraxofusp and ΔQTcF using the direct effect model.

Reviewer's comment: The reviewer did not repeat this analysis, because this is a large protein and no direct effects are expected. The sparse PK/ECG sampling time points does not support a test for acute hysteresis (within 24-h). However, no evidence of delayed effect was detected at 24 hours post-dose.

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

/s/

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08/24/2018

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08/24/2018

LARS JOHANNESEN
08/24/2018

MICHAEL Y LI
08/24/2018

CHRISTINE E GARNETT
08/24/2018

CLINICAL INSPECTION SUMMARY

Date	June 11, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D., GCPAB Team leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader, and Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emily Jen, M.D., Ph.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Kris Kolibab, Ph.D., Regulatory Project Manager Division of Hematology Products
BLA	761116
Applicant	Stemline Therapeutics, Inc.
Drug	tagraxofusp [SL-401]
NME	Yes
Therapeutic Classification/Status	recombinant human IL-3 genetically fused to a truncated DT
Proposed Indication	treatment of patients with blastic plasmacytoid dendritic cell neoplasm
Consultation Request Date	April 10, 2018
Summary Goal Date	September 15, 2018 (Priority Expedited Review)
Action Goal Date	October 30, 2018
PDUFA Date	October 30, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites (Drs. Sweet, Wang, Konopleva, and Lane) were selected by the Division of Hematology Products (DHP) for inspection in support of BLA 761116. The sponsor, Stemline Therapeutics, Inc., was also inspected. The study data from these clinical sites, as reported by the sponsor to the BLA, are considered to be reliable in support of the requested indication.

The final regulatory compliance classification for Dr. Sweet and the sponsor is No Action Indicated (NAI). The preliminary regulatory classification of Drs. Wang, Konopleva, and Lane is NAI.

2. BACKGROUND

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon hematological malignancy characterized by the clonal proliferation of malignant plasmacytoid dendritic cells. BPDCN most typically presents with skin lesions, as well as extracutaneous malignant disease in the bone marrow, blood, lymph nodes, spleen, and other organs. Despite the frequent appearance of a somewhat indolent clinical presentation at the outset, the course of BPDCN is highly aggressive and the median survival is approximately 12-14 months. There is currently no standard of care, nor an effective treatment regimen, for BPDCN.

Diphtheria toxin (DT) IL-3 fusion protein (designated SL-401 by Stemline Therapeutics, Inc. ["Stemline"]) is a targeted-biologic therapy directed to the IL-3R (IL-3 receptor). Tagraxofusp (SL-401) is comprised of recombinant human IL-3 genetically fused to a truncated DT, in which the binding domain of DT has been replaced with IL-3. The IL-3 domain of SL-401 is able to target the leukemia blasts and cancer stem cells that over-express IL-3R, leading to receptor-mediated endocytosis and localization of SL-401 to early endosomes. The translocation domain of DT changes conformation in the acidic environment of the endosome, and the RXRR motif (residues 191-194) located between the catalytic and translocation domains of DT is cleaved by endosomal furin. The translocation domain of DT then inserts into the endosomal membrane. As the TAT-like domain of DT (residues 201-230) interacts with cytosolic heat-seeking protein 90 (Hsp90) and thioredoxin reductase, the catalytic domain (A fragment) unfolds, is reduced, and translocates to the cytosol. Upon release into the cytosol, the A fragment refolds and catalytically inactivates cellular protein synthesis by ADP-ribosylating the diphthamide residue in domain IV of EF2 (an elongation factor), leading to apoptosis.

The rationale for use of the proposed treatment for BPDCN includes: 1) tagraxofusp (SL-401) fusion protein is a targeted therapy directed to the IL-3 receptor that is present on cancer stem cells and/or tumor bulk, but not on normal hematopoietic stem cells, 2) tagraxofusp (SL-401) utilizes a payload that is not cell cycle-dependent and, therefore, designed to kill not just highly proliferative tumor bulk but also relatively quiescent cancer stem cells, and 3) tagraxofusp (SL-401) utilizes a payload that may not be subject to multi-drug resistance mechanisms typically used by cancer stem cells to evade traditional therapies.

Study Protocol STML-401-0114:

Study Protocol STML-401-0114 is an ongoing multicenter Phase 1 (dose escalation) to Phase 2 (safety expansion and efficacy assessment), 4-stage, non-randomized, open-label, dose escalation and expansion, study of tagraxofusp (SL-401), for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN). A cycle of therapy is 21 days. Stages 1 thru 3 have been completed. A Data Safety Review Committee (DSRC), including sponsor representatives, review the accruing safety data and make safety decisions during the study, including dose escalations in Stage 1.

The completed Stage 3 primary objectives were to determine the complete response (CR) rate (i.e., CR + CR [clinical] with minimal residual skin abnormality [CRc]) and to characterize the safety profile of tagraxofusp (SL-401) in patients with first-line BPDCN. The primary study endpoints of interest for the review division were complete response (CR), and CR+ CRc plus CR with

incomplete blood count recovery (CRi) and include tumor treatment responses in the following regions or organs: peripheral blood, bone marrow, skin, nodes, spleen, and liver.

The 10 study sites are U.S. clinical centers. The most common individual adverse events reported to date with SL-401, regardless of dose, were ALT and AST increase, hypoalbuminemia, nausea, fatigue, pyrexia, and peripheral edema. Capillary leak syndrome, cytokine release syndrome, and infusion-related reactions are serious adverse events of particular interest to the review division.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	**Protocol # STML-401-0114// Site #/# Subjects**	**Inspection Dates**	**Classification**
Dr. Kendra Sweet H. Lee Moffitt Cancer Center & Research Institute 12902 Magnolia Dr. Tampa, FL 33612	Site #2 27 subjects enrolled	May 14 – 17, 2018	NAI
Dr. Eunice Wang Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263	Site #5 13 subjects enrolled	May 31 – June 5, 2018	Preliminary: NAI
Dr. Marina Konopleva MD Anderson Cancer Center 1515 Holcombe Boulevard Houston, TX 77030	Site #6 29 subjects enrolled	May 15 – 18, 2018	Preliminary: NAI
Dr. Andrew Lane Dana-Farber Cancer Institute 450 Brookline Ave, Mayer 413 Boston, MA 02215	Site 9 20 subjects enrolled	May 22 – 25, 2018	Preliminary: NAI
Stemline Therapeutics, Inc. 750 Lexington Avenue New York, NY 10022	Sponsor 96 Subjects	April 24 – May 1, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.

Clinical Investigator

1. Kendra Sweet, M.D.

A total of 37 subjects were screened and 27 subjects were enrolled. The study is ongoing.

The inspection evaluated the following documents: source records and worksheets (such as biopsy, bone marrow, hematology and chemistry reports), 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 20 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary efficacy study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Eunice Wang, M.D.

A total of 27 subjects were screened, and 13 subjects were enrolled. The study is ongoing.

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 the 27 screened subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary efficacy study endpoint, i.e., tumor treatment responses, were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

3. Marina Konopleva, M.D.

A total of 39 subjects were screened, and 29 subjects were enrolled. The study is ongoing.

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

Source documents for the 28 enrolled subjects, whose record were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary efficacy 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 Practice. No Form FDA 483 was issued.

4. Andrew Lane, M.D.

A total of 31 subjects were screened, and 20 subjects were enrolled. The study is ongoing.

The inspection evaluated the following documents: source records including patient drug infusion records, screening and enrollment logs, case report forms, study drug accountability logs, "in service" training records of study personnel, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for the 20 enrolled subjects, whose record were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary efficacy study endpoint, i.e., treatment responses (peripheral blood, bone marrow, skin, nodes, spleen and liver areas) 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 Practice. No Form FDA 483 was issued.

Sponsor

5. Stemline Therapeutics, Inc.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; safety reports; adverse events; protocol deviations; and standard operating procedures.

Monitoring reports indicated that the four clinical investigator study sites (i.e., Drs. Sweet, Wang, Konopleva, and Lane) received adequate periodic monitoring. There was no under-reporting of serious adverse events by the sponsor.

In general, this sponsor appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

{See appended electronic signature page}

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

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/s/

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06/11/2018

SUSAN D THOMPSON
06/11/2018