CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761116Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114513

MEETING MINUTES

Stemline Therapeutics, Inc.
Attention: Joan M. Shankle
Head of Regulatory Affairs
750 Lexington Avenue, 11th Floor
New York, NY 10022

Dear Ms. Shankle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SL-401.

We also refer to the teleconference between representatives of your firm and the FDA on February 6, 2018. The purpose of the meeting was to discuss the upcoming BLA submission for SL-401.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Kris Kolibab, PhD, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	February 6, 2018; 3:00PM – 4:00PM (EDT)
Meeting Location:	Teleconference
Application Number:	114513
Product Name:	SL-401
Indication:	Treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Sponsor/Applicant Name:	Stemline Therapeutics, Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

OHOP, Division of Hematology Products (DHP):
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Angelo de Claro, MD, Acting Deputy Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Emily Jen, MD, PhD, Clinical Reviewer
Kris Kolibab, PhD, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:
Ruby Leong, PhD, Clinical Pharmacology Team Leader
Sriram Subramaniam, PhD, Clinical Pharmacology Reviewer

Office of Biotechnology Products (OBP), Division of Biotechnology Research and Review (DBRR III):
Susan Kirshner, PhD, Review Chief
Ashutosh Rao, PhD, Chief, Laboratory of Applied Biochemistry
Baikuntha Aryal, PhD, Product Quality Reviewer
Frances Namuswe, PhD, Immunogenicity
Davinna Ligons, PhD, Immunogenicity

Office of Pharmaceutical Quality (OPQ), Division of Microbiology Assessment (DMA):
Maria Candau-Chacon, PhD, Product Quality Microbiology Team Leader

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA):
Hina Mehta, PharmD, Team Leader
Nicole Garrison, PharmD, BCPS, Safety Evaluator

Office of Biostatistics, Division of Biometrics V (DBV):
Kunthel By, PhD, Statistics Reviewer

Office of Process and Facilities:
Steven Fong, PhD, Microbiologist

SPONSOR ATTENDEES

Ivan Bergstein, MD, Acting Chief Medical Officer
Christopher Brooks, PhD, Pharmacology/Toxicology
Ronald Bowsher, PhD, Bioanalytical Methods
Janice Chen, PhD, Pharmacology/Toxicology
Joan Connolly, Manufacturing
Robert Francomano, Commercial
Trishna Goswami, MD, Senior Medical Director
Ken Hoberman, Chief Operating Officer
Joanne LaValle, Regulatory Affairs
Ross Lindsay, PhD, Immunology/Bioanalytical Methods
John Salvagno, Quality Assurance
Shay Shemesh, Clinical and Regulatory Operations
(b) (4) Biostatistics, Consultant
Biostatistics, Consultant
Pharmacometrician, Consultant
Deborah Norby, Regulatory Affairs
Joan Shankle, Regulatory Affairs, Consultant
(b) (4) Clinical, Consultant
(b) (4) Immunogenicity, Medical Consultant

1.0 BACKGROUND

SL-401 is a recombinant fusion protein comprised of human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) that is cytotoxic for IL-3R/CD123-expressing cells. Stemline is developing SL-401 for treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN). Orphan Drug designation for treatment of BPDCN was granted on June 6, 2013. Breakthrough therapy designation was granted on August 22, 2016. FDA provided advice regarding development of SL-401 at meetings or in written responses on December 14, 2014, November 22, 2016, December 20, 2016, April 28, 2017, August 1, 2017 and August 16, 2017. FDA also provided advice for preparation of the BLA submission at meetings or in written responses on September 27, 2017 and November 14, 2017.

Stemline Therapeutics requested a type B meeting with the FDA on December 5, 2017. The purpose of the meeting is to discuss the upcoming BLA submission for SL-401.

FDA sent Preliminary Comments to Stemline Therapeutics, Inc. on January 31, 2018.

2. DISCUSSION

2.1. General and/or Regulatory

Question 1:

a. As summarized in Section 11.2, establishment information for each manufacturing facility will be provided in the application and the manufacturers will be ready for inspection at the time of the BLA submission. During the discussion with FDA CMC review team in the August 16, 2017 meeting, the FDA made note that manufacturing should be ongoing during the inspection. To facilitate this with the contract manufacturers, the Sponsor requests guidance from FDA regarding possible timeframes for advance notification of intended inspection dates.

FDA Response to Question 1a:

The prelicense inspections should be conducted during the review timelines: 2 to 4 months (60 to 120 days) after the BLA submission for a priority BLA and 2 to 6 months after the submission for a standard BLA. The drug substance manufacturing facility should be in operations and manufacturing the complete product for which the biologics license is desired. For the drug product manufacturing facility inspection, all fill lines included in the BLA should be in operations either manufacturing the product under review or a surrogate product with a similar manufacturing process, (b) (4)

Discussion:

FDA clarified that in case of a rolling submission, the inspections times indicated in the response would be after the final section of the BLA was submitted. The manufacturing schedules should be included in the BLA at the time of the submission to facilitate planning of the inspections. The sponsor asked whether the drug product manufacturing facility could be manufacturing a product different to that under review during the inspection. FDA agreed as long as it is manufactured in the same line and with a similar process.

b. As summarized in Section 11.2, SL-401 received orphan drug designation for BPDCN on June 6, 2013 (Designation #13-3974). As such, the application will include a claim for the orphan exemption in the submission of the User Fee Coversheet, Form FDA 3397.24. The User Fee Coversheet will be included with the application, and a brief statement claiming the orphan exception will be included in the cover letter (Module 1.1). Is this approach consistent with FDA expectations and acceptable?

FDA Response to Question 1b:

Yes, but please also include a copy of the orphan designation letter in Module 1.12.17.

Discussion:

No discussion occurred.

c. *As noted in Section 11.4, based on the definition of a covered clinical study, Study STML-401-0114 will be the only clinical study for which financial disclosure information is provided in the BLA submission. Is this approach consistent with FDA expectations and acceptable?*

FDA Response to Question 1c:
Yes, this is acceptable.

Discussion:
No discussion occurred.

d. As noted in Section 11.5, a pediatric assessment under the Pediatric Research and Equity Act of 2003 ("PREA") is not required for SL-401 for this indication given SL-401 received orphan drug designation for BPDCN on June 6, 2013 and the BLA is to be submitted before August 18, 2020. Is this approach consistent with FDA expectations and acceptable?

FDA Response to Question 1d:
Yes.

Discussion:
No discussion occurred.

e. The safety analyses planned for BLA submission that will inform the product labeling are summarized in Section 11.6, at this time the Sponsor is seeking guidance from the review team on expectations for inclusion of information on risk minimization strategies in the BLA beyond the product labeling and routine pharmacovigilance.

FDA Response to Question 1e:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:
No discussion occurred.

f. The timing of for review of the proposed International Nonproprietary Name (INN) and proposed submission of the Proprietary Name Request are summarized in Section 11.7 and Appendix B. The Sponsor would like to discuss the proposed timing of the Proprietary Name request in the context of the timing of BLA submission and plans for

priority or expedited review and reach agreement with FDA on the appropriate timing for this submission.

FDA Response to Question 1f:

You may submit the proposed proprietary name at any time during the BLA rolling submission. The proposed proprietary name can be submitted even though your nonproprietary name is not final. A review for a proposed proprietary name submitted with a BLA will be completed within 90 days of the receipt of the submission.

Additionally, please note that you may submit your proposed proprietary name during the IND phase. A review for a proposed proprietary name submitted to the IND will be completed within 180 days of the receipt of the submission. For breakthrough designated products, the Agency targets a 90-day proprietary name review under the IND when feasible (the Agency will aim for the 90 days but cannot guarantee a 90-day review). A request for proprietary name review will also need submitted once the BLA is submitted.

Please ensure that your submission is in eCTD section "1.18 Proprietary names." On the first page of the submission, include the statement "REQUEST FOR PROPRIETARY NAME REVIEW" in bold, capital letters.

Guidance on Complete Submission for the Evaluation of Proprietary Name can be found online at:
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf

Discussion:

The Sponsor stated they plan to submit a request for review of the proposed proprietary name to the IND. The Agency informed the Sponsor that a request for proprietary name review will also need to be submitted to the BLA at any time during the rolling submission. The Sponsor acknowledged the Agency's instruction.

g. A draft table of contents for the SL-401 BLA and a draft BLA submission plan showing target dates for completion of each module and timing of a potential rolling BLA submission are provided in Appendix A and Appendix B. The Sponsor would like to discuss the proposed content and timing of BLA submission, including the proposal for a rolling review, and reach agreement with FDA on the appropriate timing for this submission.

FDA Response to Question 1g:

The proposed plan in Appendix B that describes the content and timing of the submission of portions appears reasonable, except that the Risk Management Plan needs to have a specified date rather than TBD. A request for submission of portions of an application should be sent as an amendment to the IND; attach Form FDA 1571. The amendment should be clearly

identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters. For additional information, see "Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics" at: https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

We agree with your plan to submit a 60-day safety update. Please clarify what will be in the 60-day update.

Please clarify the TBD date for submission of the process validation and stability data update. See the response to Question 5b.

Discussion:
See Discussion under Questions 5a and 5b.

h. The Sponsor requests guidance on whether the application will be designated for priority review, and if FDA plans to conduct an expedited review given the breakthrough designation, and potential for Advisory Committee meeting.

FDA Response to Question h:
You may submit a request for priority review and provide justification for your request. However, whether the application will be granted priority or expedited review will be a review issue. Whether the application warrants an Advisory Committee meeting will also be a review issue.

Discussion:
No discussion occurred.

2.2. Clinical and Statistical

Question 2:
Section 12 provides a brief summary of Study STML-401-0114 and studies to support the integrated summary of safety. The Sponsor requests confirmation that the proposed content and location(s) of documentation and datasets for Module 5 Clinical Study Reports as shown in Appendix A BLA TOC are acceptable.

FDA Response to Question 2:
We agree with your plan to submit text in Module 2.7.4 Summary of Clinical Safety (SCS) and supporting tables and figures in the ISS folder in Module 5.3.5.3. When using the SCS in lieu of the ISS, include in the SCS a review of all relevant safety data and analyses, including data from nonclinical studies, clinical pharmacology studies, studies in patients, studies in healthy volunteers, and immunogenicity studies. The SCS should show the key results that contribute to the understanding of the safety of your drug and should not simply reference the study reports. Ensure that the entire Clinical Summary (Modules 2.7.1 - 2.7.4) does not exceed 400 pages in total.

Include a letter of authorization for IND 114513. Letters of authorization for all cross-referenced INDs and Master Files should be submitted in Module 1.4.4.

We have reviewed the proposed clinical content and locations for Module 5 Clinical Study Reports, and we have the following comments:

a. Each indication should have its own folder in Module 5.3.5. Only studies pertinent to that indication should go into that folder. Studies for other indications (such as AML, etc.) should go into their own folder.

b. Please plan to include the BIMO dataset for Study STML-401-0114 in Section 5.3.5.4 with the first portion of the application submitted.

c. You propose to put CRFs in Module 5.3.7. However, there is no Module 5.3.7. in the eCTD. Please put case report forms in the related study folder.

d. Submit an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission. Refer to the Study Data Technical Conformance Guide: Technical Specifications Document for additional details.

e. Provide sufficient comments, adequate bookmarks, and hyperlinks in the define files to ensure efficient review. If you use XML version 1 for the define files, please include a pdf of the define file.

f. Provide executable SAS programs with adequate documentation to allow FDA to duplicate the analysis datasets derivation from raw datasets.

g. Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs.

Discussion:
The Sponsor agreed that the BLA submission would include the elements described in the FDA comments 2a-g above.

2.3. Clinical Pharmacology

Question 3:
a. Section 13 and Module 5 of the BLA TOC (Appendix A) provide a brief summary of the Sponsor requests review and agreement on the clinical data to be used for the clinical pharmacology analyses, and confirmation that the location of reports and datasets for each of the clinical pharmacology studies is acceptable.

FDA Response to Question 3a:
We recommend incorporating applicable clinical data with data cut-off of September 25, 2017, for the exposure-response analyses. Refer to response to Question 3b for location of the reports and datasets for clinical pharmacology analyses. In addition, given that SL-401 has a molecular weight of < 69 kDa, (b) (4) during FDA review of the proposed BLA.

Discussion:
The sponsor proposed to submit final reports and associated data sets for exposure-response analyses in the BLA submission based on data collected up to May 7, 2017. The Agency agreed with this proposal, but indicated that additional exposure-response analyses that include duration of response data may be requested during the BLA review.

b. The Sponsor requests FDA advice on whether the data tabulations from Study STML-401-0114 May 7, 2017 which support the clinical pharmacology analyses should be included in the BLA submission, and if so where.

FDA Response to Question 3b:
Yes, the reports and the associated data tabulations to support the clinical pharmacology analyses should be included in the BLA submission. The reports and the associated data tabulations to support Study STM0105F (non-compartmental PK using data from Trial STML- 401-0114) should be included in Module 5.3.3.2, and for Studies STM0103F (exposure-ECG) and STM0104F (exposure-response) should be included in 5.3.4.2. The report and the associated data tabulations for population PK Study STM0102F (using data from Trials STML-401-0114, -0214, -0314 and -0141) should be included in Module 5.3.3.5. Refer to Additional Comments a) to f) regarding preparation of the clinical pharmacology sections, communicated on September 21, 2017.

Discussion:
No discussion occurred.

2.4. Bioanalytical Methods/Immunogenicity

Question 4:
Section 14 provides a summary of the plan for Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods in the BLA submission. A listing of each method validation is provided in Appendix A BLA TOC for Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies. The Sponsor requests guidance on whether the BLA content and testing plan for analysis of samples in the BLA and ongoing clinical studies are acceptable.

FDA Response to Question 4:

Regarding bioanalytical methods for PK, a cross-validation report to support bioanalysis at the two bioanalytical sites for Trials STML-401-0114, -0214, -0314 and -0141, and bioanalytical reports for the above-mentioned trials should be provided in Module 5.3.1.4, in addition to the validation reports. Also, provide a brief description of assay performance in Trials STML-401-0114, -0214, -0314 and -0141 in Module 2.7.1, in addition to the description of methods, method validation and cross-validation.

Your proposal to submit the immunogenicity assay validation reports in Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies is acceptable. However, the content of the assay validation reports will be a review issue. Please include the standard operating procedures for all immunogenicity assays in the BLA submission. As a reminder, additional comments concerning the new IL-3 neutralizing assay were communicated to the Sponsor in the September 27, 2017 meeting minutes.

Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies and 5.3.5 Reports of Efficacy and Safety Studies. For your BLA, in addition to the information included in these sections, provide an Integrated Summary of Immunogenicity to be included in eCTD Module 5.3.5.3 Reports of Analyses of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

a. An immunogenicity risk assessment specific to your product,
b. Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods you developed in your program
c. Links to method development and validation reports for all the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your pivotal clinical study(ies)
d. Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed
e. Summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data
f. Traceability of drug product lots used in all your clinical studies
g. (b) (4)

Discussion:

The Agency stated that the cross-validation report of the bioanalytical methods for PK cannot be found in Module 5.3.1.4. The sponsor indicated that the comparability of the methods will be discussed in Module 2.7.1, and will include a link to the cross-validation report. The Agency stated that the cross-validation report should be included in

Module 5.3.1.4, in addition to the description of the comparability of the methods in Module 2.7.1.

(b) (4)

2.5. Quality

Question 5:

a. As recommend by the FDA in response to Question 3 of November 14, 2017 Type A meeting, a draft BLA TOC (Appendix A) is included with the Sponsor's proposed approach to fulfill the Agency's recommendations in the BLA submission. Does the FDA agree with the Sponsor's proposed approach to fulfill the Agency's recommendations from prior meetings?

FDA Response to Question 5a:

No, we do not completely agree with your approach. Please address the following comments in your BLA application.

i. You propose to omit some of the BLA TOC items such as excipients of human origin, novel excipients, adventitious agents etc. In your BLA you should include a statement for why these sections are not included. For example, if no materials of animal origin are used in the manufacture of your product, you should include a statement indicating that no material of animal origin are used. In addition, if you propose to include in your BLA protocols for qualification of future cell banks or future reference materials, you should specify where in the BLA the protocols will be provided.

ii. You propose to provide several important updates, such as process validation report, specifications, stability data and impurity characterization from the RP-UPLC/MS analysis during the BLA review. Provide a timeline for when you will provide such information. All product quality information required for BLA review should be provided for review at least 10 weeks prior to the action due date.

iii. Your proposed specification for container content of drug product is NLT (b) (4) mL. Provide both upper and lower limits of the amount of drug product in each vial to lower the risk for overdosing or unintended multiple use of the single-use vial.

iv. You state that you will not be able to characterize impurity 1 detected in the RP-HPLC at the time of BLA submission. Acceptability of your proposed control strategy will be a review issue based on the information provided in the application. Provide supportive

data to clarify the identity and contribution of the impurity on product quality and, as appropriate, suggest a control strategy to assure that this and other impurities are well controlled and have lot-to-lot consistency over the proposed shelf-life of the product.

v. You state that you do not intend to include the finalized drug substance and drug product validation report in the BLA application but that you will provide a comprehensive narrative. Your proposal is acceptable provided the full validation data with supporting narrative of the executed PPQ batches are included in the BLA application. Process validation reports should be available during inspection.

vi. We expect that supporting data and information for microbial control and sterility assurance be included in the BLA at the time of the submission. The supporting data and information should demonstrate microbial control of in-process hold times at scale for DS and DP. For additional expectations regarding microbial product quality and sterility assurance information to be included in the BLA submission, refer to Additional Microbiology Comments included in the response to the August 16, 2017 meeting. This information should be included in the section indicated in the Additional Comments and not cross-referenced to a Drug Masterfile.

Discussion:
The Sponsor stated that they plan to include information on adventitious agents and excipients in sections 3.2.A.2 and 3.2.A.3 of the BLA.

The Sponsor and FDA discussed the Sponsor's timeline for submission of CMC updates, including process validation reports and updated stability information. FDA clarified that the Sponsor should plan to submit process validation reports as early as possible and that all critical CMC updates, including updated stability information from PPQ batches, should be provided no later than 10 weeks from the initial submission of Module 3.

b. A summary of drug substance and drug product stability data available at time of BLA submission from both primary and supportive batches is presented in Section 15.3. The Sponsor intends to file a stability update during BLA review, and requests guidance on timing for submission of the update.

FDA Response to Question 5b:
You intend to provide stability data from the supportive batches (current clinical and engineering batches) to support the proposed shelf-life of the DS and DP but, you will not have enough primary stability data from the PPQ batches to support the proposed shelf-life of the DS (b) (4) months) and DP (b) (4) months) at the time of BLA submission. (b) (4)

As per ICH Q5C, stability data should be provided on at least 3 batches for which manufacture and storage are representative of the manufacturing scale production. Therefore,

you should provide sufficient real-time stability data from pre-PPQ and PPQ batches of DS and DP to support their proposed shelf life. In addition, if you propose to use clinical and engineering batches to support the shelf-life of DS and DP, you should provide a strong and clear justification with supportive data to demonstrate that the manufacturing and storage of the clinical and engineering batches are representative of the commercial manufacture. The shelf life of your DS and DP will be a review issue and it will be based on ICHQ5C. You may consider the submission in your BLA of a protocol for extension of shelf-life of DS or DP, which would allow you to extend shelf-life in the future as an annual reportable change.

Any stability update should be submitted to the BLA at least 10 weeks prior to the action due date. Please refer to our responses and discussion during our previous meetings on November 22, 2016 and August 16, 2017.

Discussion:
See discussion under Question 5a regarding timeline of stability data submission.

c. *As recommended by the FDA in response to our question on required leachable stability data (submitted via email on Dec. 5, 2017), additional detail on the extractable and leachable program is provided in Section* ***Error! Reference source not found.*** *and Appendix C. Does FDA agree that it is acceptable to place one PPQ batch on a prospective leachable stability study to supplement the aged product data provided to date?*

FDA Response to Question 5c:
Yes, your proposed leachable/extractable study for a PPQ batch appears to be reasonable based on the background information provided in the meeting package. However, the acceptability of your control strategy will be a review issue after assessment of your leachable/extractable study including your risk assessment that includes the product contact materials, study design, and full leachable/extractable results.

Discussion:
No discussion occurred.

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor stated a request for rolling review will be submitted to the IND. Agency acknowledged the request and will provide a response when the submission is reviewed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. The Sponsor suggested that a REMS is not needed. Agency acknowledged the Sponsor's conclusion and informed the Sponsor this will be a review issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Sponsor stated that they intend to submit a complete application; therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

a. Number of subjects screened at each site
b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

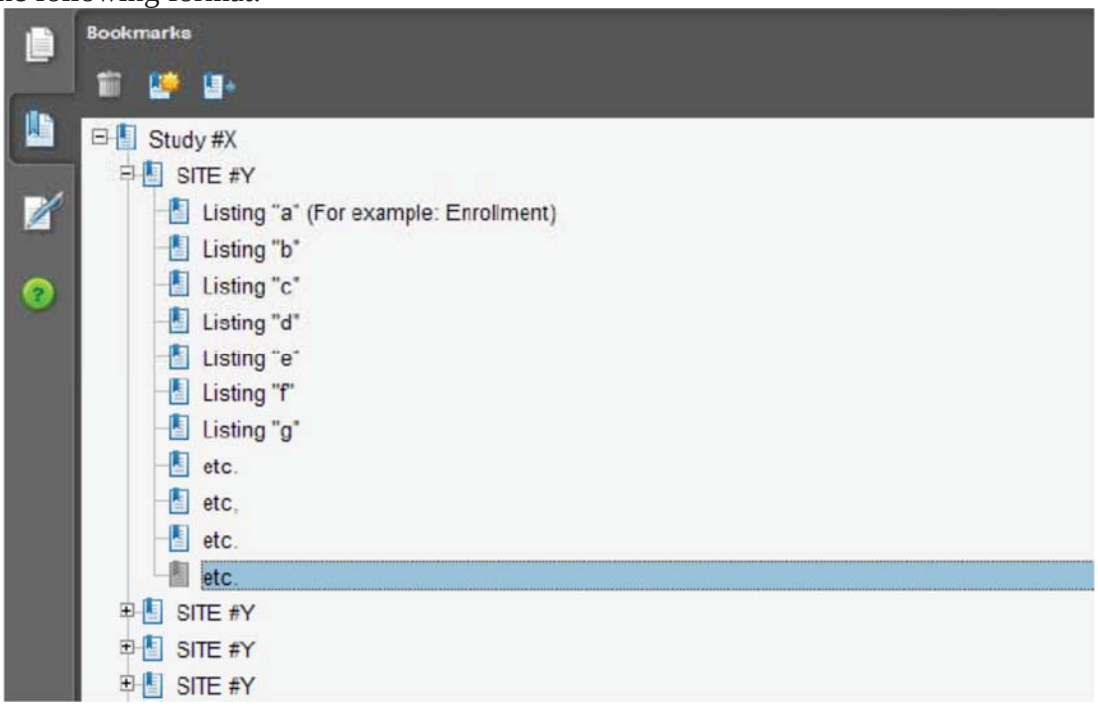
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached handouts for the teleconference.

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

DONNA PRZEPIORKA
02/27/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	**IND 114513**
Request Receipt Date	6/29/16
Product	SL-401 (DT388-IL3, Diphtheria Toxin Interleukin-3 Fusion Protein)
Indication	Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
Drug Class/Mechanism of Action	Immunotoxin directed at the IL-3 receptor (CD123)
Sponsor	Stemline Therapeutics, Inc.
ODE/Division	OHOP / DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	8/28/16

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Treatment for patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

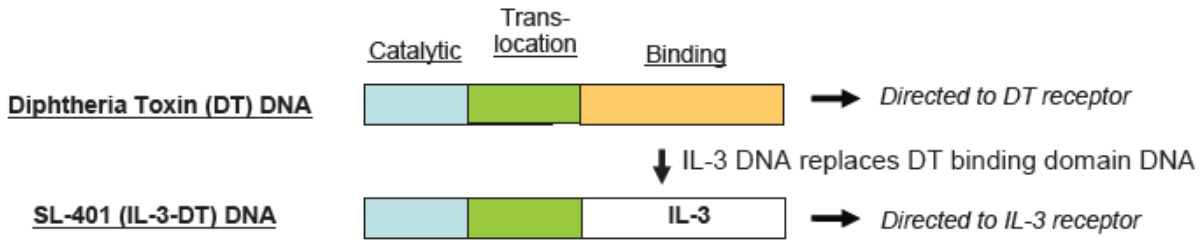
[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

a. *SL-401* (DT388-IL3) is a diphtheria toxin (DT)-interleukin-3 (IL-3) fusion protein (Figure 1) which acts by targeting DT to cells that express the IL-3 receptor. Once internalized, DT mediates cytotoxicity by inactivation of eEF-2 and inhibition of protein synthesis, resulting in cell death independent of cell cycling.

Figure 1. Schematic of SL-401 Constuct



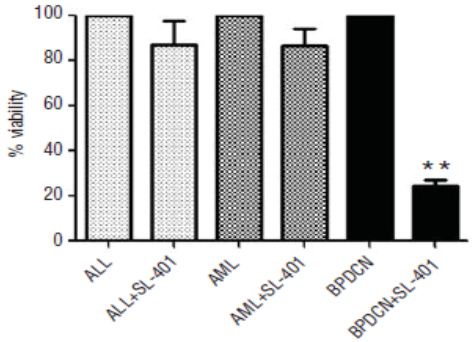
Source: IB Figure 3-1

b. *BPDCN* is an aggressive hematologic malignancy thought to be derived from type 2 dendritic cells. Most commonly it affects older adults (median age at diagnosis 67 years), usually manifesting as cutaneous lesions with or without bone marrow involvement and leukemic dissemination. Patients present with indolent skin lesions and rapidly progress to leukemic manifestations; a subset may present with leukemia and no cutaneous lesions. Diagnosis is based on morphological criteria and expression of CD4, CD43, CD56 and well as the plasmacytoid dendritic cell-associated antigens CD123 (IL3RA), BDCA-2/CD303, TCL1 and CTLA as described in the WHO 2008 classification. Prior to 2008, when CD123 expression was not commonly assessed, this entity may have been classified as an NK cell leukemia, blastic NK cell lymphoma, or hematodermic neoplasm. The actual incidence is unknown, but it has been estimated to account for <1% of leukemias or lymphomas (Pagano 2016).

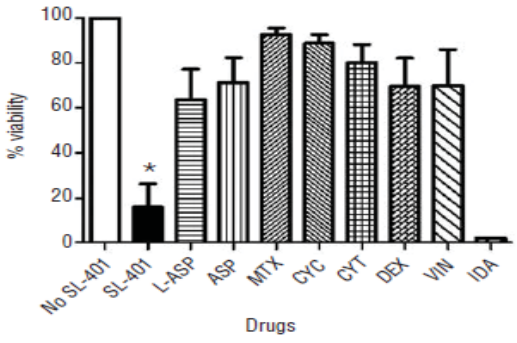
c. The *rationale of use of SL-401 for treatment of BPDCN* comes from preclinical data which showed that BPDCN cells were highly sensitive to SL-401 *in vitro* in comparison to AML or ALL cells (Figure 2), only idarubicin was more inhibitory than SL-401 (Figure 2), and cytotoxicity was dose-dependent.

Figure 2. In vitro effects of SL-401:

a) Effect of SL-401 on viability of blast cells from patients with ALL, AML or BPDCN.



b) Effect of SL-401 or chemotherapeutic drugs on viability of blast cells from patients with BPDCN.



Source: Angelot-Delettre 2015 Figures 2 amd 3

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

(b) (4)

[redacted]

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

There are no established response criteria for BPDCN. Durable CR has been used to support accelerated approval for acute leukemia, and durable CR+PR for lymphoma. Endpoints for regular approval include OS for acute leukemia and PFS or OS for lymphoma. In rare cases, a substantial rate of highly durable responses might be sufficient to support regular approval. Primary sites of BPDCN include skin and bone marrow, and secondary sites include lymph nodes, other viscera, and the CNS, so neither the acute leukemia nor the lymphoma response criteria alone would be applicable. CR is the preferred endpoint.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

There are no FDA-approved therapies for BPDCN.

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Multiagent chemotherapy, including regimens used to treat AML, ALL and NHL, are used for treatment of BPDCN. There are no prospective trials of chemotherapy. The sponsor provided a literature review of retrospective experience in patients treated afterter the 2008 WHO designation of this disease as BPDCN.

Table 2: Sponsor's Review of Published Complete Response Rates in First-line BPDCN

Author	Footnote	N (Primary Report)	Response criteria	Reported CR rate	Adjusted CR rate
Empirical first-line treatment outcomes from largest retrospective primary series (≥30 patients) since 2008 WHO classification of BPDCN					
Poret 2015		86	not reported	43%	43%
Dalle 2010		47	not reported	47%	47%
Martin-Martin 2015	1	46	not reported	72%	55%
Pagano 2013	2	43	AML	41%	37%
Pemmaraju 2015	3	37	AML	51%	51%

1 High early death rate (26%). CR rate includes patients who received treatment (irrespective of whether they completed treatment). Adjusted CR rate (55% [23/42]) includes an additional 10 patients who received "palliative treatment". Four included cases were pediatric.
2 High death rate (17%) during induction therapy. A total of 15/41 (37%) patients achieved CR with induction chemotherapy; 2 partial responders subsequently became complete responders with consolidation therapy (17/41: 41%).
3 Median age 62 yrs. Includes 10 patients previously reported (Pemmaraju 2012).
Adjusted CR refers to results for adults alone.

The weighted CR rate is 50%, and the weighted adjusted CR rate is 46%. The reported median relapse-free survival (RFS) ranged from ~5 to 9 months for patients who initially responded to therapy

9. **A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].**

None.

10. **Information related to the preliminary clinical evidence:**

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Results were submitted from two Phase 1 studies with expansion cohorts. STML-401-0114 was conducted by the sponsor, and Study 50047 was an investigator-initiated trial. Table 3 shows the key elements of the study designs and the preliminary results.

Table 3: Studies of SL-401 for Patients with BPDCN

	STML-401-0114	**Study 50047**
Sponsor	Stemline (IND 114513)	Investigator-initiated (IND 011314)
Plan		
Design	Phase 1 single-arm, multicenter, dose-escalation and expansion	(b) (4)
Eligible population	BPDCN, untreated high-risk AML or relapsed/refracotry AML	
Treatment schedule	Days 1-5 of each 21-day cycle	
Treatment duration	Until disease progression or toxicity	
Planned sample size - Total	Up to 104 in both stages	
Planned sample size - BPDCN	Up to 50 patients with BPDCN, including 40 treated at the RP2D as first-line therapy	
Primary endpoint	ORR per protocol definition	
Hypothesis	None	
Analysis plan	Descriptive; no interim analysis planned	
Results		
RP2D	12 mcg/kg on days 1-5	
Total Accrual	64	
Patients with BPDCN	24	
Evaluable patients with BPDCN treated at the RP2D	18 (13 males and 5 females) Median age 66 yers (range, 29-78 yrs)	
ORR	16/18 (89%)	
First-line therapy	n=12	
Exposure	Median 6 cycles (range, 3-14+)	
Response	7/12 (58%) CR 4/12 (33%) CRc+CRi 1/12 (8%) PR	
Response duration	Median RFS not reached (range, 2+ - 13+) (Median follow-up 6 mos)	
Relapsed/refractory	n=6	
Exposure	~3 cycles	
Response	1/6 (17%) CRc (no CR) 3/6 (50%) PR	
Response duration	Median follow-up only 2 mos; the 1 CRc patient maintains the response for 6+ mos.	

(b) (4)

In addition to the studies in adults described above, the sponsor also reported on a 15 year-old girl with BPDCN relapsed and refractory to two salvage chemotherapy regimens. She achieved a PR when treated with SL-401.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*

There are no approved therapies, so the results with SL-401 (summarized in Table 4) provides preliminary evidence of of a therapeutic advance. Additionally, the CR rate of single agent SL-401 as first line therapy appears similar to the historical experience with unapproved multiagent leukemia/lymphoma-type therapy.

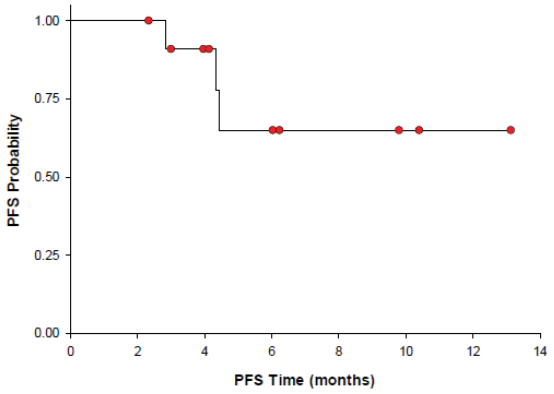
Table 4: Response rates for first-line treatment of BPDCN

	Response Category	n	Result
FDA-approved drugs	There are no approved drugs	-	-
Off-label use of combination chemotherapy	Weighted CR rate from sponsor's literature review	259	50%
SL-401: Study STML-401-0114	CR	12	58% (95% CI, 28%-85%)
[redacted] (b) (4)			

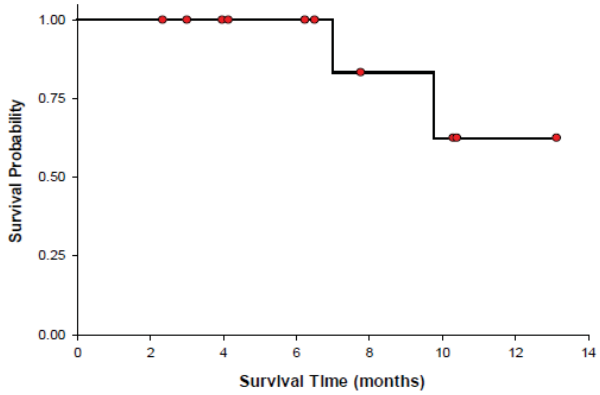
[redacted] (b) (4) Further, the durability of the response is supported by the progession free survival of 2+ to 13+ months; median PFS was not reached in Study STML-401-0114 with a median of 6 months of follow-up (Figure 3). The small number of subjects treated with SL-401, and the relatively short follow-up are potentially dissuasive, but the magnitude of the single-agent treatment effect and reproducibility across studies offsets these negatives, especially in the absence of any approved therapies.

Figure 3: Study STML-401-0114 - Outcomes of first-line treatment of BPDCN

a) Progression-free survival



b) Overall survival



Source: Sponsor's analysis

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

a) [redacted] (b) (4)

b) Eleven (85%) of 13 patients studied had SL-401 reactive antibodies (ADA) with a median titer of 800 prior to drug administration; presumably these are anti-DT antibodies due to childhood immunization to DT. After treatment, the median titer rose as high as 800,000. Of 10 patients studied for NAb, 4 (40%) were positive at baseline, and 9 (90%) were positive at one time point or more posttreatment. Current evidence suggests that systemic free drug exposure is less in Cycle 3 than in Cycle 1, likely related to the high incidence and titers of anti-DT antibodies. At this time, the impact of circulating ADA on total drug (free SL-401 + antibody-bound SL-401) exposure remains unclear. The sponsor is developing an assay to measure total SL-401 and enable quantitative determination of both the free and bound forms of SL-401. The results of the ADA studies may help determine whether ADA have a negative impact on PD and response, and clarify the feasible duration of therapy.

c) (b) (4)

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

(b) (4) Data were presented for 23 patient with BPDCN treated under IND114513 (Table 5).

Table 5: Study STML-401-0114 – Adverse events in patients with BPDCN treated with SL-401

	All TEAEs		Treatment-related TEAEs	
MedDRA Preferred Term	All Grades N=23 n (%)	≥Grade 3 N=23 n (%)	All Grades N=23 n (%)	≥Grade 3 N=23 n (%)
At least 1 TEAE	20 (87)	19 (83)	17 (74)	16 (70)
Alanine aminotransferase increased and/or alanine aminotransferase increased	17 (74)	14 (61)	15 (65)	13 (57)
Alanine aminotransferase increased	16 (70)	11 (48)	13 (57)	10 (43)
Aspartate aminotransferase increased	15 (65)	11 (48)	15 (65)	11 (48)
Nausea	12 (52)	0	6 (26)	0
Thrombocytopenia/platelet count decreased	11 (48)	11 (48)	5 (22)	(22)
Fatigue	10 (43)	2 (9)	(26)	0
Hypoalbuminaemia	10 (43)	0	10 (43)	0
Oedema peripheral	10 (43)	0	4 (17)	0
Pyrexia	10 (43)	0	9 (39)	0
Chills	9 (39)	0	8 (35)	0
Anaemia	7 (30)	4 (17)	4 (17)	3 (13)
Hyperglycaemia	7 (30)	2 (9)	2 (9)	1 (4)
Hypocalcaemia	7 (30)	1 (4)	1 (4)	1 (4)
Weight increased	7 (30)	0	5 (22)	0
Constipation	6 (26)	0	1 (4)	0
Dyspnoea	6 (26)	1 (4)	1 (4)	1 (4)
Hyponatraemia	6 (26)	3 (13)	2 (9)	1 (4)
Insomnia	6 (26)	0	0	0
Asthenia	5 (22)	0	2 (9)	0
Capillary leak syndrome	5 (22)	2 (9)	5 (22)	(9)
Decreased appetite	5 (22)	0	4 (17)	0
Headache	5 (22)	0	1 (4)	0
Hypokalaemia	5 (22)	0	1 (4)	0
Hypotension	5 (22)	0	5 (22)	0

Source: Sponsor's analysis

Capillary leak syndrome is the most troublesome toxicity of SL-401. Five (22%) of the 23 patients with BPDCN were reported to have capillary leak syndrome, including Grade 2 in intensity for 3 patients, Grade 4 for 1 patient, and Grade 5 for 1 patient. The protocol was amended to exclude patients with left ventricular ejection fraction (LVEF) below the institutional lower limit of normal, and to provide additional clinical criteria for which SL-401 infusions should be withheld. No severe or serious cases of CLS have occurred among patients with BPDCN after these precautions were implemented.

The most common TEAE for patients with BPDCN was transaminase elevation (74% any grade, and 61% grade 3 or higher), which was largely transient. The median time to onset of grade 3 ALT increase was 6 days, and the median duration was 8.5 days.

Of note, denileukin difitox (IL-2 conjugated to diphtheria toxin), a DT-immunotoxin approved for the treatment of recurrent cutaneous T-cell lymphoma, has box warnings for (b) (4) capillary leak syndrome and loss of visual acuity and color vision. Changes in visual acuity and color vision were not specifically assessed in patients treated with SL-401 on Study STML-401-0114 .

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

BPDCN is a life-threatening condition. There are no FDA-approved treatments for BPDCN. The preliminary clinical evidence demonstrates that SL-401 may provide a reasonable chance of complete remission in this population.

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The very low incidence of BPDCN is likely to make a prospective randomized trial impracticable. DHP would recommend that the sponsor submit an application for full approval based on durable CR in a sing;e-arm trial. Study STML-401-0114 is an exporatory trial, and there are no other trials planned at this time. DHP plans to meet with the sponsor to discuss key elements of a pivotal trial of SL-401, including a) the optimal duration of treatment given the potential impact of ADA on PK and/or response, b) the response definition that would describe a clinical benefit, c) identification of a sample size and an hypothesis to justify the sample size, d) analysis of response by subgroup, especially leukemia-predominant vs skin-predominant presentation, e) prospective monitoring for loss of visual acuity and color vision, and f) sufficient follow-up to determine whether liver toxicity from SL-401 alters the risk of VOD after subsequent allogeneic stem cell transplantation.

13. List references, if any:

Frankel AE, Woo JH, Ahn C, Pemmaraju N, Medeiros BC, Carraway HE, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood 2014;124(3):385-392.

Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. Br J Haematol. 2016;174(2):188-202.

Pagano L, Valentini CG, Pulsoni A, Fisogni S, Carluccio P, Mannelli F, et al. for the GIMEMA-ALWP (Gruppo Italiano Malattie EMatologiche dell'Adulto, Acute Leukemia Working Party). Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica. 2013;98(2):239-46.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

PATRICIA A DINNDORF
08/24/2016

DONNA PRZEPIORKA
08/24/2016

ANN T FARRELL
08/24/2016