CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION MEMORANDUM

CLINICAL STUDIES

NDA/BLA #:	BLA 761-116
Supplement #:	NME
Drug Name:	Elzonris™ (Tagraxofusp)
Indication(s):	Treatment of patients with blastic plasmacytoid dentritic cell neoplasm (BPDCN)
Applicant:	Stemline Therapeutics
Submission Date:	June 21, 2018
PDUFA Date:	December 21, 2018
Review Priority:	Priority review with an expedited timeline
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Cindy Gao, Ph.D.
Concurring Reviewers:	Yuan-Li Shen. Dr. P.H., Team Leader
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Medical Division:	Division of Hematology Products
Clinical Reviewer:	Emily Jen, M.D.
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Keywords: blastic plasmacytoid dentritic cell neoplasm (BPDCN); response rate; Kaplan-Meier

Background

The applicant submitted the results of the pivotal Study STML-401-0114 to support the application of SL-401 (ElzonrisTM [Tagraxofusp]) for the treatment of patient with blastic plasmacytoid dentritic cell neoplasm (BPDCN).

BPDCN is an uncommon and highly aggressive hematologic malignancy with poor prognosis with a median survival of approximately 8 to 14 months from diagnosis. There is currently no approved therapy or standard of care for patients with BPDCN who are treatment-naïve or who have been previously-treated.

The pivotal study STML-401-0114 (i.e., Study 0114) is a multi-stage, nonrandomized, open-label, multicenter study of SL-401 in BPDCN and AML patients divided into 4 stages. The study was initiated in Jun 2014 and ongoing at the time of the submission.

The patient population in each stage are summarized as follows
Stage 1 - patients with first-line or R/R BPDCN or AML
Stage 2 - patients with first-line or R/R BPDCN or AML
Stage 3 - first-line BPDCN patients only
Stage 4 - patients with first-line or R/R BPDCN

The primary objective of each stage is summarized as follows
Stage 1 – to determine the maximum tolerated dose (MTD).
Stage 2 – to determine the efficacy of SL-401 in BPDCN patients, as assessed by objective response rate (ORR) and characterize the safety profile of SL-401 at MTD in both patients with AML and BPDCN.
Stage 3 – to determine the CR rate (CR + CR with minimal residual skin abnormality [CRc]) and characterize the safety profile of SL-401 in patients with first line BPDCN.

The primary efficacy endpoint is CR rate (CR + CRc) using the Investigator's response determinations, in first-line BPDCN patients in Stage 3, accompanied by an evaluation of the durability of response, as a key secondary endpoint in this cohort.

The other secondary endpoints include

- Bone marrow complete response (BMCR) and duration of BMCR for Stage 3 (additional analysis includes BMCR and duration in Stage 1-4). BMCR rate was measured by patients who had either CR or PR according to the response criteria who achieved reduction to $\leq$ 5% BM blast cells, as a proportion of all patients with marrow disease (> 5% BM blast cells) at baseline.
- CR (CR + CRc) rate and duration of CR for Stage 1 and 2
- CR (CR + CRc) rate and duration of CR for pooled data from Stages 1, 2 and 3
- ORR (CR + CRc + CRi + PR) and duration of objective response for Stages 1 and 2
- ORR (CR + CRc + CRi + PR) and duration of objective response for pooled stages

- Proportion of patients who received SCT for pooled data from all stages
- PFS for all stages pooled
- OS for all stages pooled

The sample size for the pivotal cohort Stage 3 was determined based on the lower bound of a 2-sided 95% confidence interval of the CR rate to rule out the reference rate of 10%. Assuming a CR rate of at least 60%, a minimal sample size of 10 first-line BPDCN patients provided at least 90% power for the primary efficacy assessment.

For the timing of the analysis, in accordance with agreement with FDA in the Type B meeting on 20 Dec 2016, first-line BPDCN patients enrolled on or after 26 Oct 2016 were considered as a separate, pivotal patient cohort for statistical analysis (i.e, Stage 3). The cutoff date for analysis of data for the primary efficacy analysis was 25 Sep 2017. All surviving patients enrolled into Stage 3 included in this data submission had at least 6 months of follow-up.

The primary analysis population for analysis of efficacy is modified intent-to-treatment (mITT) population, defined as all patients who were eligible based on the screening criteria and who received at least 1 dose of SL-401.

For analysis methods, response rate with 95% CI based on Clopper-Pearson Exact method would be presented with 10% as the benchmark for comparison. Time-to-event endpoints would be analyzed with Kaplan–Meier method. BMCR rate was measured by patients who had either CR or PR according to the response criteria who achieved reduction to ≤ 5% BM blast cells, as a proportion of all patients with marrow disease (> 5% BM blast cells) at baseline.

The analysis was done separately for first-line patients and for relapse/refractory patients, even though all the patients were enrolled at the same time in this pivotal study STML-401-0114. The analysis focused on those patients who received a dose 12 ug/kg/day based on sponsor's intent to use this dose.

Study Patients

Disposition of Patients

Overall, the study enrolled 32 patients (19 patients in stage 1 and 2; 13 patients in stage 3) with treatment naive BPDCN, and 15 patients (13 patients in stage 1 and 2; 2 patients in stage 4) with relapsed/refractory (R/R) BPDCN.

Table 1 Patient Enrollment for Patients with BPDCN

	Stage 1 N	**Stage 2 N**	**Stage 3 N**	**Stage 4 N**	**Overall N**
First Line BPDCN					
12 ug/kg/day	3	13	13	0	29
7 ug/kg/day	3	0	0	0	3
R/R BPDCN					

12 ug/kg/day	3	10	0	2	15
7 ug/kg/day	0	0	0	0	0

Source: adapted from Table 10-1, Clinical Study Report, Study 0114

For first-line treatment of BPDCN, patients' enrollment and disposition are summarized in Table 2. As of the data cut off date, of the 32 first-line BPDCN patients, 2 were ongoing in the study. Of the 30 patients who had discontinued by this time, 12 were discontinued because of PD; 12 were discontinued for "other" reasons; 4 were discontinued at the Investigator's discretion; and 2 patients discontinued because of an AE. Of the 12 patients discontinuing for "other" reasons, 11 had been/were being bridged to SCT and the remaining patient discontinued SL-401 to receive an alternate treatment.

Table 2 Patient Disposition: First-line BPDCN

	Stage			
Parameter	**1 (N=6) n (%)**	**2 (N=13) n (%)**	**3 (N=13) n (%)**	**Overall (N=32) n (%)**
Total Number of Patients:				
Treated	6 (100)	13 (100)	13 (100)	32 (100)
Ongoing on Treatment at Data Cutoff[1]	0	2 (15.4)	0	2 (6.3)
Study Populations:				
Modified Intent-to-Treat Population	6 (100)	13 (100)	13 (100)	32 (100)
Safety Population	6 (100)	13 (100)	13 (100)	32 (100)
Immunogenicity Population	6 (100)	13 (100)	13 (100)	32 (100)
Discontinued Study	6 (100)	11 (84.6)	13 (100)	30 (93.8)
Primary Reason for Discontinuation				
Disease Recurrence/ Progression	3 (50.0)	5 (38.5)	4 (30.8)	12 (37.5)
Physician Decision	0	1 (7.7)	3 (23.1)	4 (12.5)
Adverse Event	1 (16.7)	0	1 (7.7)	2 (6.3)
Other[2]	2 (33.3)	5 (38.5)	5 (38.5)	12 (37.5)
Received SCT Since Discontinuation[3]				
Yes	2 (33.3)	8 (61.5)	8 (61.5)	18 (56.3)
Allogeneic	1 (16.7)	5 (38.5)	7 (53.8)	13 (40.6)
Autologous	1 (16.7)	2 (15.4)	0	3 (9.4)
RIC Allogeneic	0	0	1 (7.7)	1 (3.1)
Other	0	1 (7.7)	0	1 (3.1)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; RIC = Reduced Intensity Conditioning; SCT = Stem Cell Transplant.
1 25 Sep 2017
2 Of the 12 patients discontinuing for "other" reasons, 11 had been/were being bridged to SCT and the remaining patient discontinued SL-401 to receive an alternate treatment (Listing 16.2.1.1).
3 Patients who reported any SCT after treatment with SL-401 were included (ie, including patients bridged to SCT [N=13] and those who had progression on study and then received subsequent SCT [N=5]).

Source: Table 10-2, Clinical Study Report, Study 0114

For R/R BPDCN, patients' enrollment and disposition are summarized in Table 3. All 15 patients received the dose of 12 ug/kg/day, and all these patients completed participation as of the data cutoff date. Of these 15 patients, 11 discontinued due to PD and 1 withdrew consent to participate. Three patients discontinued for "other" reasons, including subsequent SCT for 2 patients and patient preference for the remaining patient.

Table 3 Patient Disposition: Relapsed/Refractory BPDCN

	Stage			
	1	2	4	Overall
Parameter	(N=3) n (%)	(N=10) n (%)	(N=2) n (%)	(N=15) n (%)
Total Number of Patients:				
Treated	3 (100)	10 (100)	2 (100)	15 (100)
Ongoing on Treatment at Data Cutoff	0	0	0	0
Study Populations:				
Modified Intent-to Treat Population	3 (100)	10 (100)	2 (100)	15 (100)
Safety Population	3 (100)	10 (100)	2 (100)	15 (100)
Immunogenicity Population	3 (100)	10 (100)	2 (100)	15 (100)
Discontinued Study	3 (100)	10 (100)	2 (100)	15 (100)
Primary Reason for Discontinuation				
Disease Recurrence	2 (66.7)	7 (70.0)	2 (100)	11 (73.3)
Withdrawal of Consent	1 (33.3)	0	0	1 (6.7)
Other[1]	0	3 (30.0)	0	3 (20.0)

Source: Table 14.1.1B.
1 Of the 3 patients discontinuing for "other" reasons, reasons included subsequent SCT for 2 patients (1 directly after SL-401 and 1 after receiving alternate therapy after SL-401), and patient preference (Listing 16.2.1.1).

Source: Table 10-3, Clinical Study Report, Study 0114

Dataset Analyzed

Within the mITT population, the review focused on the 32 first-line patients and 15 R/R patients who received SL-401 at 12 ug/kg/day. The median time since BPDCN diagnosis is 1.2 month in the first line patients and 1 year for R/R patients.

Demographic and Baseline Characteristics

Most patients were male and white. The median age is 68 years in first line patients and 72 years in R/R patients. All patients have ECOG score 0 or 1.

Table 4 Demographic and Baseline Characteristics

	First-Line (N = 32)	**R/R** (N = 15)
Gender		

Male	26 (81.3%)	13 (86.7%)
Female	6 (18.8%)	2 (13.3%)
Race		
White	30 (93.8%)	13 (86.7%)
American Indian or Alaska Native	1 (3.1%)	2 (13.3%)
Other	1 (3.1%)	0
Age		
Mean (SD), years	63.0 (16.0)	69.0 (10.8)
Median (range), years	67.5 (22, 84)	72 (44, 80)
ECOG performance		
0	17 (53.1%)	5 (33.3%)
1	15 (46.9%)	10 (66.7%)
Time since BPDCN diagnosis (months)		
Mean (SD)	1.65 (1.91)	21.1 (22.0)
Median (range)	1.20 (0, 10.4)	12.0 (2.6, 84.4)
BPDCN at Baseline		
Bone marrow disease	15 (46.9%)	9 (60.0%)
Peripheral blood disease	7 (2.9%)	1 (6.7%)
Skin disease	31 (96.9%)	13 (86.7%)
Lymph node disease	13 (40.6%)	8 (53.3%)
Visceral disease	4 (12.5%)	4 (26.7%)

Source: reviewer analysis

Efficacy Results

In this efficacy summary, data from 29 patients (16 in Stages 1 and 2; 13 in Stage 3) who received 12 ug/kg/day (the intended dose) will be summarized. During the review, the FDA clinical reviewer Dr. Jen adjudicated the response and the sponsor agreed with Dr. Jen's adjudication results. Therefore, the efficacy results in the following are based on Dr. Jen's adjudication results.

For the first line treatment, the CR rate (CR+CRc) together with the duration of CR are summarized in Table 4. In Stage 3, the CR+CRc rate is 53.8% (95% CI, 25.1%, 80.8%). The median follow-up time is 26 months for stage 1 and 2, 11.5 months for stage 3, 17.6 months for all stages (by Kaplan-Meier method). The median duration of response was not estimable for patients who achieved CR+CRc.

Note that the result of PFS and OS is not reported here because the study is a single arm study and therefore PFS and OS is not interpretable. It is noted that the median OS time for both Stage 1 or 2 and Stage 3 have not reached yet.

Table 5 Efficacy in First Line BPDCN (12 μg/kg/day, FDA's adjudication)

	Stage 1 and 2 N = 16	**Stage 3** N = 13	**All Stages** N = 29
Primary Endpoint			
CR+CRc rate, n/N (%) (95% CI)	14/16 (87.5) (61.7, 98.4)	7/13 (53.8) (25.1, 80.8)	21/29 (72.4) (52.8, 87.3)
Secondary Endpoints			
Duration of CR+CRc, median (95% CI), month	NE (1.5, NE)	NE (7.3, NE)	NE (5.9, NE)
Less than 6 months, n/N	7/14	1/7	8/21
Between 6 months and 1 year, n/N	1/14	5/7	6/21
Longer than 1 year, n/N	6/14	1/7	7/21
ORR, n/N (%) (95% CI)	16/16 (100.0)	10/13 (76.9) (46.2, 95.0)	26/29 (89.7) (72.7, 97.8)
Duration of OR, median (95% CI), month	NE (2.2, NE)	NE (0.7, NE)	NE (2.5, NE)
Less than 6 months, n/N	7/16	4/10	11/26
Between 6 months and 1 year, n/N	2/16	5/10	7/26
Longer than 1 year, n/N	7/16	1/10	8/26
BMCR, n/N (%)	7/7 (100)	6/6 (100)	13/13 (100)

Source: reviewer analysis

For the patients with R/R BPDCN, the efficacy is summarized in Table 6. Among the 15 patients, two patients reached CR/CRu (13.3%, 95% CI, 1.7%, 40.5%), and the duration of these two responses are 3.6 and 13.9 months respectively. The follow up time ranged from 18 days to 17.2 months, with a median of 6.6 months. It is noted that the median OS time was 7.1 months (95% CI, 4.1, 11.9). However, OS in a single arm study is not interpretable.

Table 6 Efficacy in R/R BPDCN (12 μg/kg/day, FDA adjudication)

	Previously Treated N = 15
Primary Endpoint	
CR+CRc rate, n/N (%) (95% CI)	2/15 (13.3) (1.7, 40.5)
Secondary Endpoints	
Duration of CR+CRc, months	3.7 and 13.9
ORR, n/N (%) (95% CI)	10/15 (66.7) (38.4, 88.2)
Duration of OR, median (95% CI)	1.6 (0.7, 3.6)

Source: reviewer analysis

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Summary

The applicant submitted the results of the Study 0114 for approval of SL-401 for the treatment of BPDCN.

- Evaluation of efficacy for the first line treatment focused on 29 patients with 13 patients in the pivotal cohort Stage 3. The complete response rate (CR+CRc) is 53.8% (95% CI, 25.1%, 80.8%) in Stage 3 patients and 72.4% (95% CI, 52.8%, 87.3%) in patients of all stages. The duration of response was not estimable in either stage 3 patients or all stages patients.

- Evaluation of efficacy for the R/R treatment was based on 15 patients. Two patients who achieved complete response (CR+CRc) (13.3%, 95% CI, 1.7%, 40.5%) with duration of response is 3.7 and 13.9 months respectively.

No major statistical issue was identified in the review. The judgment of whether a favorable result of SL-401 treatment is demonstrated will be based on the risk-benefit assessment for patients with BPDCN and is deferred to clinical decision.

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/

YUAN L SHEN on behalf of XIN GAO
11/19/2018

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11/19/2018

RAJESHWARI SRIDHARA
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