CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761116Orig1s000

SUMMARY REVIEW

Office Director Decisional Memo
Division Director Summary Review for Regulatory Action
Cross-Discipline Team Leader Review

Date	12/21/2018
Office Director (or designee)	Richard Pazdur, MD
Division Director (or designee)	Ann T. Farrell, MD
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
Application Number / Type	**BLA 761116 / Original 351(a)**
Applicant	Stemline Therapeutics, Inc.
Date of Submission	6/21/2018
PDUFA Goal Date	2/21/2018
Proprietary Name	Elzonris
Proper Name	Tagraxofusp-erzs
Dosage Form(s)	Injection (1,000 mcg in 1 mL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication	For the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older
Recommended Dosing Regimen	12 mcg/kg intravenously on days 1 to 5 of a 21-day cycle until disease progression

Additional Reviews Consulted	**Discipline Reviewer(s)**
OPQ (12/7/2018)	Steven Bowen, PhD; Rong Wang, PhD: Baikuntha Aryal, PhD; Davina Ligons, PhD; Vicky Hemphill-Borders, PharmD; Steven Fong, PhD; Maria Lopez-Barragan, PhD; Monica Commerford, PhD; Reyes Candau-Chacon, PhD
Pharmacology Toxicology (11/26/2018)	Natalie E Simpson, PhD; Christopher M Sheth, PhD
Clinical Pharmacology (11/21/2018)	Liang Li, PhD; Luning Zhuang, PhD; Ruby Leong, PharmD.; Chao Liu, PhD.
Clinical (11/23/2018)	Emily Jen, MD, PhD
Statistical (11/19/2018)	Cindy Gao, PhD; Yuan-Li Shen, DrPH
Regulatory Project Manager (7/5/2018)	Kristopher Kolibab, PhD
Deputy Director for Labeling (DHP) (9/12/2018)	Virginia E. Kwitkowski, MS, ACNP-BC
IRT (8/24/2018)	Moh Jee Ng, MS; Dalong Huang, PhD; Nan Zheng, PhD; Michael Y Li, MS; Lars Johannesen, PhD;
OPDP (12/11/2018)	Rachel Conklin, MS, RN
OSE/DMEPA (7/9/2018; 11/14/2018; 11/21/2018; 11/29/2018)	Nicole Garrison, PharmD,; Casmir Ogbonna, PharmD, MBA; Carlos M Mena-Grillasca, PharmD; Hina Mehta, PharmD
OSE/DRISK (11/30/2018)	Till Olickal, PhD, PharmD: Elizabeth Everhart, MSN, ACNP
OSI (6/11/2018)	Anthony Orencia, MD, FACP

1. Benefit-Risk Assessment

BLA 761116 was submitted under 351(a) for the new molecular entity tagraxofusp-erzs, a CD123-directed cytotoxin. The indication proposed by the Applicant was "For the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)."

The review team recommended regular approval for the indication "For the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older" using tagraxofusp-erzs 12 mcg/kg/day on days 1-5 of a 21-day cycle until disease progression.

Evidence of clinical benefit came from Study STML-401-0114 a multicenter, multicohort, single-arm trial of tagraxofusp-erzs for adults with BPDCN or acute myeloid leukemia (AML). The primary efficacy endpoint of the analyses was complete response (CR) and clinical CR (CRc), the latter of which included minimal residual skin abnormalities. In the absence of established response criteria for this rare disease, the clinical meaningfulness of this novel endpoint was assessed by qualification in the patients in the initial cohorts of the study and affirmed by FDA prior to analysis of the pivotal cohort.

The Stage 3 cohort of Study STML-401-0114 was designed to exclude a 10% CR+CRc rate in patients with untreated BPDCN. The CR+CRc rate in this pivotal cohort of 13 patients was 54% (95% CI: 25, 81), and the median duration of CR+CRc was not reached with a median follow-up of 11.5 months (95% CI: 8.8, 11.9). The lower 95% bound of the CR+CRc rate exceeded 10%, so the study is considered positive. The relatively high point estimate of the CR+CRc rate (54%) and the durability of the response was considered clinically meaningful.

An additional response analysis was conducted in 15 patients with relapsed or refractory BPDCN pooled from the other stages of Study STML-401-0114. This exploratory analysis showed a CR+CRc rate of 13% (95% CI: 2, 41); the 2 responses seen lasted 3.6 and 13.9 months. (b) (4) [redacted] the positive results in the pivotal cohort, the results for the patients with relapsed or refractory BPDCN are considered credible.

Safety of the recommended dose and schedule of tagraxofusp-erzs was assessed in 94 patients with active BPDCN or AML. Capillary leak syndrome (CLS) occurred in 55% of patients, and it was fatal in 2%. Other major safety issues included hypersensitivity reactions and hepato-toxicity. The risk of these serious events was controlled in the clinical trial by close monitoring and guidelines for dose modification and supportive care which will need to be included in labeling. These events also warrant warnings, including a boxed warning for CLS. The most common (incidence ≥30%) adverse reactions were CLS, nausea, fatigue, peripheral edema, pyrexia and weight increase. The most common (incidence ≥ 10%) Grade ≥ 3 laboratory abnormalities were platelets decreased, hemoglobin decreased, neutrophils decreased, glucose increased, ALT increased and AST increased.

Safety data were also available for one child and two adolescents treated for BPDCN. The safety profile of tagraxofusp-erzs in the pediatric patients was similar to that in adults. With safety data in the pediatric patients and extrapolation of efficacy from adults, the intended population can be extended down to age 2 years.

Nearly all patients had antidrug antibodies (ADA) by the end of Cycle 2 of therapy with tagraxofusp-erzs. The 68% incidence of treatment-emergent anti-IL-3 antibodies is a concern, especially since patients may proceed to hematopoietic stem cell transplantation, and the effect of such antibodies on post-transplant hematopoietic recovery is not clear. Further information will be sought by enhanced pharmacovigilance for reports of graft failure or delayed engraftment in the postmarketing period.

Considering the severity of BPDCN and the absence of approved therapies, and with the risk mitigation strategies in place, the evidence supports the conclusion that the clinical benefit from treatment with tagraxofusp-erzs outweighs the expected risks for patients with BPDCN.

Benefit Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• BPDCN is a very rare but aggressive hematological malignancy.	BPDCN is a fatal disease.
Current Treatment Options	• There are no approved therapies for BPDCN. • There are no consensus guidelines for treatment of BPDCN.	There is a need for an effective agent to treat BPDCN.
Benefit	• STML-401-0114 was a multicenter, single-arm trial of tagraxofusp-erzs 12 mcg/kg/day on days 1-5 of a 21-day cycle. • In the prospective cohort of 13 patients with newly-diagnosed BPDCN, the CR+CRc rate was 54% (95% CI: 25, 81). • For the retrospective cohort of 15 patients with relapsed or refractory BPDCN, the CR+CRc rate was 13% (95% CI: 2, 41). • The responses were durable.	There is substantial evidence that tagraxofusp-erzs is active in patients with newly-diagnosed or relapsed/ refractory BPDCN based on durable CR+CRc.
Risks and Risk Management	• Capillary leak syndrome (CLS) occurred in 55% and is potentially fatal. • Other clinically significant adverse reactions included hypersensitivity and hepatotoxicity. • The most common adverse reactions were CLS, nausea, fatigue, peripheral edema, pyrexia and weight increase. • Development of neutralizing ADA was common.	The overall short-term safety profile of tagraxofusp-erzs is acceptable for the intended population with clinical and laboratory monitoring to minimize risks and with appropriate warnings, including a boxed warning for CLS.

Patient experience data were not submitted as part of this application.

Donna Przepiorka, MD, PhD
Cross-Discipline Team Leader

2. Background

2.1 Product Information

Proposed Trade Name:	Elzonris™
Established Name:	Tagraxofusp-erzs
Also Known As:	SL-401, DT388IL3, Molecule 129
Molecular Weight:	57.7 kDaltons
Dosage Forms:	Injection (1,000 mcg in 1 mL)
Therapeutic Class:	Antineoplastic
Chemical Class:	Recombinant protein
Structure:	Fusion protein comprised of a recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT)
Pharmacologic Class:	CD123-directed cytotoxin
Mechanism of Action:	Inhibits protein synthesis and causes cell death in CD123-expressing cells

2.2 Therapeutic Context

Except where noted, the following information is taken from the Clinical Review.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy with a dendritic cell derivation. Diagnostic criteria for BPDCN were formalized in the WHO 2008 guidelines.[1] Diagnosis is based on morphological criteria and expression of surface markers including CD123 (IL-3R alpha), CD4, and CD56. BPDCN is estimated to account for < 1% of leukemias or lymphomas.[2] The median age at diagnosis is 53 years, but a bimodal distribution age distribution was reported.[3] There is a male predominance in adults. Clinically, the disease manifests in skin, marrow, lymph nodes, spleen, spinal fluid, liver or other viscera. No prognostic factors have been identified.[4]

There are no drugs approved for treatment of BPDCN. For patients with newly-diagnosed BPDCN, the current standard of care is induction with an intensive multiagent acute leukemia

[1] Facchetti F, et al. (2008) Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, Swerdlow SH, E Campo, NL Harris, et al (editors), IA RC, p.145.
[2] Pagano L, et al. (2013) Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 98:239-246.
[3] Guru Murthy GS, et al. (2018) Epidemiology and survival of blastic plasmacytoid dendritic cell neoplasm. Leuk Res 73:21-23. .
[4] Falcone U, et al. (2016) A critical review of treatment modalities for blastic plasmacytoid dendritic cell neoplasm. Crit Rev Oncol/Hematol 107:156-162.

regimen followed by allogeneic stem cell transplantation in first remission. There is no agreed upon best induction regimen, although response rates appear to be higher with ALL-like regimens than with AML-like regimens.[4] The complete remission rates reported have varied from 25% to 100%, but the number of patients in each series is small, so the reliability of the point estimates of remission are questionable; moreover, there are no consensus response criteria. The median overall survival in adults diagnosed with BPDCN is approximately 7-14 months.[4,5] There are no systematic studies of treatment of relapsed or refractory BPDCN.

2.3 Regulatory Background

The full regulatory history is described in detail in Section 3.2 of Dr. Jen's review. The following information is relevant to this submission in particular.

Tagraxofusp-erzs was developed under IND 114513 which was received by FDA on 6/27/2014. Orphan Designation for treatment of blastic plasmacytoid dendritic cell neoplasm was granted on 6/6/2013, and Breakthrough Therapy Designation for the treatment of blastic plasmacytoid dendritic cell neoplasm was granted on 8/22/2016. FDA provided the Applicant with advice regarding the development program at eight formal meetings or in writing. Key advice for the clinical development included:

- (b) (4) Conduct of an adequate and well-controlled study of a pivotal cohort that addresses a specific indication and intended population is needed. *[Type B Breakthrough Developmental Meeting 12/20/2016]*

- In the absence of qualified response criteria, CR with durability would be the preferred measure of clinical benefit in a single-arm trial for BPDCN. *[Type C meeting 12/16/2014; Type B Breakthrough Developmental Meeting 12/20/2016]*

- The analyses of response and durability in the exploratory cohort were sufficient to qualify CR+CRc with durability as an acceptable measure of clinical benefit for BPDCN at this time. *[Type A meeting 11/14/2017]*

The FDA agreed with a rolling submission of the BLA on 3/8/2018. BLA 761116 was submitted in parts with the first part received 4/4/2018 and the final complete BLA received on 6/21/2018. The BLA was filed 60 days thereafter with a Priority review classification. The Midcycle Communication was held on 10/3/2018, and the Late Cycle Meeting was held on 11/15/2018.

Tagraxofusp-erzs is not approved or marketed in any other countries.

[5] Kim MJM, et al. (2017) Pediatric blastic plasmacytoid dendritic cell neoplasm: A systematic literature review. J Pediatr Hematol Oncol 39:528--537.

3. Product Quality

Except where noted, the following information is taken from the Product Quality Assessment.

Tagraxofusp-erzs drug substance is manufactured by recombinant technology in *E. coli* from a single hybrid gene. The 524-amino acid tagraxofusp-erzs recombinant protein consists of an N-terminal methionine followed by diphtheria toxin (DT) residues 1-388 (Q388R variant) with the catalytic and translocation domains of DT followed by a His-Met dipeptide linker to the N-terminus of the full 133-amino acid sequence of human IL-3. All impurities were within acceptable limits, and the updated drug substance release and stability specifications provide adequate control over the CQAs of tagraxofusp-erzs DS to ensure product consistency as determined by the drug substance Product Quality Reviewer Potency is based on a cytotoxicity assay using TF-1hRas cells which express the IL-3 receptor. The dating period is (b) (4) months at (b) (4)

Elzonris injection drug product is a preservative-free, sterile, clear, colorless solution supplied as 1,000 mcg in 1 mL in a single-dose glass vial. The drug product formulation includes (b) (4) sodium chloride (75 mM), sorbitol (50 (b) (4) mg), (b) (4) and Water for Injection, USP. The container closure system is a single-use, 2.0 mL (b) (4) glass vial with a 13-mm gray (b) (4) stopper and a 13-mm flip-off seal. The dating period is 36 months at (b) (4) protected from light. This product is exempted from lot release per Docket No 95-29960.

The drug product Product Quality Reviewer noted that the product formulation used in the clinical studies is consistent with the proposed commercial drug product formulation. Therefore, all clinical study data are applicable to the to-be-marketed formulation.

One drug substance facility (b) (4) and one drug product (b) (4) facility were inspected. Both inspections were classified as Voluntary Action Indicated (VAI) with Form 483 observations issued. The Applicant submitted adequate responses to the Form 483 observations within this review cycle. All involved manufacturing facilities were considered acceptable. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(c).

The Product Quality Reviewers found that the information submitted is sufficient to support a conclusion that the manufacturing process of Elzonris drug product is well-controlled and leads to a product that is pure and potent for the duration of the product shelf life. OPQ recommended approval under conditions specified in labeling. They also recommended five postmarketing commitments (PMCs) to improve the robustness of the DS manufacturing processes (see Section 13.2).

4. Nonclinical Pharmacology/Toxicology

The following information is taken from the Nonclinical Pharmacology/Toxicology Review.

4.1 Primary Pharmacology

Tagraxofusp-erzs was shown to bind human IL-3RA with a Kd of 470 nM, which is comparable to human IL-3 binding to IL-3RA (hIL-3 Kd 670 nM). Submitted and published data support the mechanism of action of tagraxofusp, which upon binding to IL-3RA, is internalized and increases ADP ribosylation of elongation factor-2 (EF-2). It is widely accepted that ADP-ribosylation of EF-2 by DT blocks the ability of EF-2 to facilitate protein synthesis. (b) (4)

In vitro, tagraxofusp-erzs reduced cell proliferation and increased expression of apoptotic markers in BPDCN cell lines and in blasts from patients with BPDCN. The correlation between sensitivity to tagraxofusp-erzs and CD123 receptor density was mixed. In mouse xenograft models of BPDCN, tagraxofusp-erzs increased overall survival compared to controls.

4.2 Nonclinical Toxicology

One-month (i.e., 1 cycle) and 3-month (i.e., 3 cycle) GLP-compliant toxicity studies were conducted in cynomolgus monkeys with doses of up to 60 mcg/kg/day for 5 days. Neutralizing antibodies were detected in this species. At human equivalent doses greater than or equal to 1.6 times the recommended dose based on body surface area, severe kidney tubular degeneration or necrosis was observed. At human equivalent doses equal to the recommended dose, necrosis or degeneration of the choroid plexus in the brain was observed in cynomolgus monkeys. Clinical signs included hunched posture, tremors, decreased activity, eyes partially or completely closed and hypersensitivity. The reversibility of this finding was not assessed at lower doses, but the finding was irreversible and became progressively more severe at a human equivalent dose 1.6 times the recommended dose 3 weeks after dosing stopped.

Additional toxicities noted included inappetence and body weight decrease, reduced thymus weights, lymphoid depletion, increased liver weight, hepatocellular vacuolation, mineralization of the ovaries in females, dry/scabbing skin, and minimal to mild perivascular hemorrhage or necrosis at the injection site. Laboratory abnormalities included decreased reticulocytes, prolonged coagulation times, increased basophils, increased neutrophils, increased globulin, increased fibrinogen, decreased albumin, increases in ALT and AST, increased BUN and creatinine, decreased phosphorus and calcium, and proteinuria.

No genetic toxicology, carcinogenicity, or reproductive and developmental toxicology studies were conducted. Based on its mechanism of action, tagraxofusp-erzs has the potential for adverse effects on embryo-fetal development and may cause fetal harm when administered to

a pregnant woman, and the Nonclincal Reviewer recommended that this be communicated clearly in labeling.

5. Clinical Pharmacology

The Applicant submitted data from four early phase clinical trials (see Appendix 14.1) and three pharmacometrics reports applicable to the clinical pharmacology of tagraxofusp-erzs. Except where indicated, the following information is taken from the Clinical Pharmacology Review of these studies.

5.1 Pharmacokinetics

The pharmacokinetics evaluation in patients with BPDCN showed:

- Following administration of tagraxofusp-erzs 12 mcg/kg via 15-minute infusion, the mean (SD) area under the plasma drug concentration over time curve (AUC) was 231 (123) hr·mcg/L and maximum plasma concentration (Cmax) was 162 (58.1) mcg/L.

- The mean (SD) volume of distribution of tagraxofusp-erzs was 5.1 (1.9) L.

- The mean (SD) clearance was 7.1 (7.2) L/hr, and the mean (SD) terminal half-life was 0.7 (0.3) hours.

- The presence of ADAs had a meaningful effect on the pharmacokinetics of tagraxofusp-erzs. The AUC and Cmax were reduced by 34.6% and 50.6%, respectively, and clearance was increased by 1.96-fold in patients with pre-existing ADA versus the patients without pre-existing ADA (see Section 5.3 below).

With regard to specific populations:

- No clinically significant differences in the pharmacokinetics of tagraxofusp-erzs were observed based on age, sex, mild or moderate renal impairment, mild or moderate hepatic impairment, or body weight after adjusting dose by body weight.

- The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), or severe hepatic impairment (total bilirubin >3 times ULN and any AST) on tagraxofusp-erzs pharmacokinetics is unknown.

With regard to the drug-drug interactions:

- No drug-drug interaction studies have been conducted with tagraxofusp-erzs.

5.2 Pharmacodynamics

Time-matched sampling of tagraxofusp-erzs and ECG data were collected on Study STML-401-0114. Consistent with the product class, the IRT Reviewer identified no clinically meaningful effect of tagraxofusp-erzs on QTcF, PR or QRS in outlier or central tendency analyses. The Clinical Pharmacology reviewer recommended [redacted] (b) (4)

5.3 Immunogenicity

The Immunogenicity Reviewer found that the screening, confirmatory, and neutralizing assays were validated adequately. Among 130 patients treated with tagraxofusp-erzs in the four clinical trials:

- 96% (115/120) of patients evaluable for the presence of pre-existing anti-drug antibodies (ADAs) at baseline before treatment were confirmed positive with 21% being positive for the presence of neutralizing antibodies. The high prevalence of ADAs at baseline was anticipated due to diphtheria immunization.
- 99% (107/108) of patients evaluable for treatment-emergent ADA tested positive with most patients showing an increase in ADA titer by the end of Cycle 2.
- 85% (86/101) of ADA-positive patients evaluable for the presence of neutralizing antibodies were neutralizing antibody-positive.
- 68% (73/108) of patients evaluable for treatment-emergent anti-IL-3 antibodies tested positive with most patients testing positive by Cycle 3.

The Clinical Pharmacology Reviewer reported that the pre-existing antibodies correlated inversely with Cycle 1 Day 1 AUC with even more reduced AUC for Cycle 3 Day 1 as shown in the table below.

Free Tagraxofusp-erzs Concentration by ADA Titer

	AUC_{last} (h•µg/L)					
	Cycle 1 Day 1 (N = 77)			Cycle 3 Day 1(N = 31)		
ADA Titer	N	Mean	StD	N	Mean	StD
Not Detected	5	183	130	1	0.246	--
1	1	1.42	--	--	--	--
8	3	208	109	--	--	--
80	12	162	57.3	--	--	--
800	37	66.6	69.7	1	6.14	--
8000	16	32.9	57.4	2	0	--
80000	3	3.96	2.84	9	1.71	2.64
800000	--	--	--	16	1.11	2.30
8000000	--	--	--	2	0	--

Abbreviations: AUC_{last} = AUC from time 0 to last quantifiable observation; StD = standard deviation
Note: (Study 0114; May 7, 2017 Data Cutoff)

Source: Summary of Clinical Pharmacology Studies, Figure 1.

The Clinical Pharmacology Reviewer also noted a lower response rate and higher adverse reaction rate in patients with pre-existing ADA as shown in the table below.

Effect of Neutralizing Antibodies on Efficacy and Safety

	Treatment-naïve BPDCN (N = 25)		Relapsed/refractory BPDCN (N = 13)		
	Baseline NAb+ to post-trt NAb+ (n = 6)	Baseline NAb- to post-trt NAb+ (n = 19)	Baseline NAb+ to post-trt NAb+ (n = 3)	Baseline NAb- to post-trt NAb+ (n = 8)	Baseline NAb- to post-trt NAb- (n = 2)
CR+CRc Rate % [95% CI]	17 [0.4, 64]	74 [49, 91]	0	25 [3, 65]	50 [1, 99]
Grade ≥ 3 TEAEs % [95% CI]	67 [22, 96]	81 [58, 95]	67 [9, 99]	88 [47, 100]	100 [16, 100]

Source: Dr. Li's Table 2

5.4 Dose Considerations

For the patients in Study STML-401-0114, the Pharmacometrics Reviewer found a relationship between tagraxofusp-erzs exposure and best overall response that was of borderline significance statistically. Significant exposure-response relationships were also found with capillary leak syndrome, hypoalbuminemia, and elevated transaminases. The Clinical Pharmacology Reviewer concluded that tagraxofusp-erzs 12 mcg/kg intravenously over 15 minutes daily on days 1 to 5 of a 21-day cycle was acceptable on the basis of clinical safety.

The Clinical Pharmacology Reviewer also addressed the question of whether the development of neutralizing antibodies would negate any efficacy of multiple cycles of therapy. He noted that the IC50 of tagraxofusp-erzs is approximately 6 logs below the LLOQ for the measurement of tagraxofusp-erzs in plasma. Therefore, the measurable exposure may not be a reliable indicator of potential activity in vivo, and there are no available data that support restricting the treatment duration in the absence of a safety issue.

This BLA was considered approvable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical - Efficacy

The following information is taken largely from the Statistical Review and the Clinical Review.

7.1 Issues Related to the Clinical Development Program

The indication proposed by the Applicant for tagraxofusp-erzs is "for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)."

The Applicant submitted efficacy and/or safety data from four sponsored clinical trials (outlined in Appendix 14.1). Study STML-401-0114 is the only clinical trial used in the analysis of efficacy. FDA frequently requires multiple trials to establish efficacy. At the Breakthrough Therapy Developmental meeting on 12/20/2016, FDA recommended that in addition to the extant Cohorts 1 and 2 of Study STML-401-0114, the Applicant should conduct an adequate and well-controlled single-arm trial with a sample size sufficient to exclude a response rate that would not be clinically meaningful for the intended population and with follow-up sufficient to assess durability of the response. Cohort 3 of Study STML-401-0114 was added to meet that advice.

7.2 Issues Related to Study STML-401-0114

STML-401-0114 was a multicenter, open-label, single-arm trial evaluating the safety and efficacy of tagraxofusp-erzs monotherapy in four cohorts:

Stage 1 – Dose escalation
- Population: BPDCN or R/R AML
- Primary objective: To determine the maximum tolerated dose (MTD)
- Treatment: Tagraxofusp-erzs 7, 9, 12 or 16 µg/kg/day x 5 days of a 21-day cycle

Stage 2 - Dose expansion
- Population: BPDCN or R/R AML
- Primary objective: To determine the efficacy in subjects with BPDCN as assessed by ORR and to characterize the safety profile.
- Treatment: Tagraxofusp-erzs 12 µg/kg/day x 5 days of a 21-day cycle

Stage 3 – Pivotal cohort supporting BLA
- Population: Newly-diagnosed BPDCN
- Primary objective: To determine the CR+CRc rate
- Treatment: Tagraxofusp-erzs 12 µg/kg/day x 5 days of a 21-day cycle

Stage 4 – Expanded access cohort
- Population: BPDCN
- Treatment: Tagraxofusp-erzs 12 µg/kg/day x 5 days of a 21-day cycle

A sample size of 10 patients was calculated to have 90% power to target a 60% CR+CRc rate and exclude a 10% rate using a two-sided 95% Clopper Exact confidence interval. Since the determination of eligibility required central review that could be delayed, it was specified that

up to 15 patients could be included in the analysis population if enrolled within the enrollment period.

The following issues were considered regarding the design of Cohort 3:

- The recommended Phase 2 dose of tagraxofusp-erzs 12 µg/kg/day x 5 days of a 21-day cycle was based on the MTD in Cohort 1 and confirmed in Cohort 2. This dose was found to be acceptable.
- Prior to this study, there were no established response criteria for BPDCN. The clinical benefit measure was complete response (CR) (no evidence of disease in marrow, blood, skin, node, spleen and liver) or CR with minimal residual skin abnormality (CRc). The latter required clearance of ≥ 75% of a patient's skin lesions from baseline and ≤ 10% residual overall with only hyperpigmentation or abnormality not indicative of active disease on a biopsy (or no biopsy performed). Following review of data from Cohorts 1 and 2 to qualify the clinical meaningfulness of CRc at a Type A meeting on 11/14/2017, FDA accepted the endpoint of CR+CRc. See Section 7.1.1 of Dr. Jen's review for further discussion.
- Although statistically accurate, the sample size of 10 patients is quite small for an assessment of efficacy. However, considering the rarity of the disease, the lack of available therapy, the projected size of the treatment effect, and the supporting data from the exploratory cohorts, the design was considered acceptable.

7.3 Issues Related to the Analysis of Efficacy

STML-401-0114: Efficacy Results

	Newly-Diagnosed BPDCN		**R/R BPDCN**
	Pivotal Cohort (Stage 3) N = 13	**(Stages 1 - 2) N = 16**	**Exploratory N = 15**
CR+CRc (95% CI)	7 (54%) (25, 81)	14 (88%) (62, 98)	2 (13%) (2, 41)
Median CR+CRc Duration (mos) (95% CI)	NE (7.3, NE)	NE (1.5, NE)	(3.7 and 13.9 mos)
CR (95% CI)	3 (23%) (6, 54)	9 (56%) (31, 79)	1
CRc (95% CI)	4 (31%) (10, 61)	5 (31%) (12, 59)	1

Source: Statistical Reviewer's Tables 5 and 6 and Clinical Reviewer's Table 13.

The pivotal cohort included 13 patients of median age 65 years (range, 22-84 years) with newly-diagnosed BPDCN; 11 (85%) were male and all were Caucasian. Organ involvement included skin in 100%, marrow in 54%, lymph nodes in 46% and viscera in 15%. At the time of analysis of the pivotal cohort for newly-diagnosed BPDCN, the patients had been treated with a median of 4 cycles (range, 1-8), all patients were off therapy, and all patients had at least 6 months of

follow-up or discontinued early. Six patients (46%) had gone on to allogeneic HSCT with CR or CRc. The median follow-up time was 11.5 months. The table above shows the efficacy outcomes using responses as adjudicated by the Clinical Reviewer. The median time to response was 2 months (range, 0.5-3.5 months). The Kaplan-Meier duration of response was not estimable; the observed duration of response was 11.0+ months (range, 6.5+ to 12.6+ months). Other than the readjudication of responses, there were no major issues in the analysis of efficacy for the pivotal cohort. The small number of patients precluded conduct of a meaningful subpopulation analysis.

There were 15 patients of median age 72 years (range, 44-80 years) with relapsed or refractory BPDCN; 87% were male and 87% were Caucasian. At the time of analysis all patients were off therapy. The patients had been treated with a median of 3 cycles (range, 1-7). One patient (6%) went on to allogeneic HSCT with CR or CRc. The table above shows the response rate and duration of responses for the patients with relapsed or refractory BPDCN.

7.4 Efficacy Conclusions

The lower 95% bound of the CR+CRc rate in the pivotal cohort with newly-diagnosed BPDCN exceeded 10%, so the study is considered positive. The point estimate of the CR+CRc rate is 54%, and this is considered clinically meaningful. The results in the supportive cohort with newly-diagnosed BPDCN are consistent with the pivotal cohort outcomes, but the supportive cohort patients were included in part in the qualification of the efficacy endpoint, (b) (4)

Although FDA does not usually approve new drugs based on outcomes from an exploratory study, the cohort with relapsed or refractory BPDCN represents a distinct population whose response results would be of value to the healthcare providers. (b) (4) the positive results in the pivotal cohort, the results for the patients with relapsed or refractory BPDCN are considered credible and should be included in labeling.

Lastly, the Clinical Reviewer identified no biological differences in BPDCN in adults vs children. Therefore, it is concluded that the efficacy seen in adults can be extrapolated to the pediatric population.

8. Safety

The following information is taken largely from the Clinical Review.

8.1 Safety Database

Safety data were available for 162 patients exposed to tagraxofusp-erzs in 4 commercial clinical trials listed in Appendix 14.1. The full safety database for review was limited to 97 males and 42 females of median age 67 years (range, 21-87 years) with active myeloid neoplasm

(BPDCN 44%, AML 35% or a myeloproliferative neoplasm 21%). The exposure by dose is shown in the table below.

Full Safety Database - Exposure by Dose

Dose	N	Median months (range)	0 to 3 months	> 3 to 6 months	> 6 to 12 months	> 12 months
5-Day Schedule						
7 µg/kg/day	6	2.4 (0.2-13.5)	3 (50%)	2 (33%)	-	1 (17%)
9 µg/kg/day	3	0.8 (0.2-3.6)	2 (67%)	1 (33%)	-	-
12 µg/kg/day*	94	1.4 (0.1-30.5)	70 (74%)	20 (20%)	2 (2%)	2 (2%)
16 µg/kg/day	7	0.0 (0.1-1.1)	7 (100%)	-	-	-
3-Day Schedule						
7 µg/kg/day	3	0.8 (0.8-0.8)	3 (100%)	-	-	-
9 µg/kg/day	3	1.0 (0.8-13.4)	2 (67%)	-	-	1 (33%)
12 µg/kg/day	23	2.9 (0.1-11.4)	13 (57%)	6 (26%)	4 (17%)	-
Total	139	1.5 (0-30.5)	100 (72%)	29 (21%)	6 (4%)	4 (3%)

Source: Dr. Jen's Table 17
*Safety Population

The 94 patients treated with tagraxofusp-erzs 12 µg/kg x 5 days of a 21-day cycle comprised the Safety Population. The demographics of the safety population are shown in the table below.

Safety Population - Demographics

	BPDCN N = 58	AML N = 36	Pooled N = 94
Sex			
Female	8 (14%)	14 (39%)	22 (23%)
Male	50 (86%)	22 (61%)	72 (77%)
Age (Years)			
Median (Range)	69 (22-84)	63 (21-87)	66.5 (21-87)
18 - <65 years	22 (38%)	19 (53%)	41 (44%)
65 - <75 years	22 (38%)	9 (25%)	31 (33%)
≥ 75 years	14 (24%)	8 (22%)	22 (23%)
ECOG			
0	25 (43%)	5 (14%)	30 (32%)
1-2	32 (55%)	30 (83%)	62 (66%)
Unknown	1 (2%)	1(3%)	2 (2%)
Race			
White	52 (90%)	33 (92%)	85 (90%)
Black	2 (3%)	2 (6%)	4 (4%)
Asian	2 (3%)	1 (3%)	3 (3%)
Other	2 (3%)	-	2 (2%)
Treatment Status			
Untreated	42 (72%)	1 (3%)	43 (46%)
Relapsed/refractory	16 (28%)	32 (89%)	48 (51%)

Source: Dr. Jen's Table 19

The Clinical Reviewer concluded that the size and composition of the safety population were adequate to identify and estimate the incidence of adverse reactions to tagraxofusp-erzs, but the data base submitted did not include pediatrics patients. The Applicant did submit written materials that described safety of tagraxofusp-erzs in three children with BPDCN as summarized in Section 8.3 below.

8.2 Issues Related to Major Safety Events

Capillary Leak Syndrome

The main safety issue for tagraxofusp-erzs was capillary leak syndrome (CLS). The Clinical Reviewer identified five patients in the safety database with CLS as the root cause of death and one patient where CLS may have contributed to death. Using the PT Capillary leak syndrome, the Applicant report an incidence of 18%. However, when CLS was defined as the onset of 2 or more signs and symptoms of CLS within 7 days of each other, the incidence was 55% (52/94), including Grade 1 or 2 in 46% (43/94), Grade 3 in 6% (6/94), Grade 4 in 1% (1/94) and 2 fatal events (2/94, 2%). Common (incidence ≥ 20%) signs and symptoms associated with CLS that were reported during treatment with tagraxofusp-erzs include hypoalbuminemia, edema, weight gain, and hypotension. The median time to CLS was 4 days (range, 1-96 days). Most patients could be managed by withholding tagraxofusp-erzs and administering albumin with or without diuretics or steroids, but four patients required vasopressors, three required ventilator support and two required dialysis. The severity of this adverse reaction warrants a boxed warning and clear instructions for monitoring and early intervention.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in 46% (43/94) of patients treated with tagraxofusp-erzs and were Grade ≥ 3 in 10% (9/94). Manifestations reported in ≥ 5% of patients include rash, pruritus, stomatitis, and wheezing. The severity of this adverse reaction warrants a warning and instructions for monitoring and early intervention.

Hepatotoxicity

Elevations in transaminases were common in patients treated with tagraxofusp-erzs, occurring in 88% (83/94) of patients, including Grade 1 or 2 in 48% (45/94), Grade 3 in 36% (34/94) and Grade 4 in 4% (4/94). Most events occurred in Cycle 1 (days 7-10), and most resolved by withholding tagraxofusp-erzs. A second peak of transaminase elevations was noted days 28-35 in some patients with visceral involvement of BPDCN. There were two cases that met Hy's law criteria, but both had additional potential etiologies for the enzyme abnormalities. Nonetheless, to prevent a higher risk of drug-induced liver abnormalities in the postmarketing period, this adverse reaction warrants a warning and instructions for monitoring and early intervention.

Immunogenicity

See Section 5.3 for the discussion of the impact of ADA on safety outcomes.

Dose-Related Adverse Reactions

The analysis of adverse reactions by tagraxofusp-erzs dose (7-16 mcg/kg/day for 5 days) demonstrated no new safety signal, but as seen in the table below, several key adverse reactions occurred more frequently with the 5-day vs the 3-day regimen of 12 mcg/kg/day.

Key Cycle 1 Grade ≥ 3 Adverse Reactions in Cycle 1 by Schedule

	5-day Regimen (BPDCN/AML) N = 94		**3-day Regimen (MPN) N = 36**	
Adverse Reaction	**n**	**%**	**n**	**%**
Any Grade ≥ 3	79	84%	22	61%
Elevated LFTs	37	39%	1	3%
Thrombocytopenia	27	29%	1	3%
Neutropenia	22	23%	5	14%
CLS	11	12%	3	8%

Source: Dr. Jen's Section 8.7.1

The 5-day schedule of tagraxofusp-erzs 12 mcg/kg/day appears to have more toxicity than the 3-day schedule. Of interest, the Clinical Reviewer calculated that most patients in Stages 1-3 of Study STML-401-0114 did not receive 5 doses of tagraxofusp-erzs in Cycle 1, and only 68% received 4 doses. Nonetheless, the efficacy results were achieved using the 5-day regimen, and it appears to be tolerated by some with monitoring and intervention as needed, so to avoid recommending a regimen without proven efficacy, labeling should match the regimen as tested in the clinical trial.

8.3 Issues Related to Common Adverse Reactions

Common Adverse Reactions

The table below shows the adverse reactions that occurred in at least 10% of patients treated with tagraxofusp-erzs in the safety population. The most common (incidence ≥30%) adverse reactions were capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, weight increase, and headache.

Safety Population - Common Adverse Reactions

	N=94	
	All Grades %	**Grade ≥ 3 %**
Capillary leak syndrome	55	9
Nausea	49	0
Fatigue	45	7
Peripheral edema	43	1
Pyrexia	43	0
Weight increase	31	0
Hypotension	29	9
Chills	29	1
Headache	29	0
Decreased appetite	24	0
Constipation	23	0
Vomiting	21	0
Diarrhea	20	0
Dizziness	20	0
Febrile neutropenia	20	18
Back pain	20	2
Dyspnea	19	2
Insomnia	17	0
Tachycardia	17	0
Hypertension	15	6
Anxiety	15	0
Cough	14	0
Epistaxis	14	1
Oropharyngeal pain	12	0
Confusional state	11	0

Source: Dr. Jen's Section 8.5

Common Laboratory Abnormalities

The table below shows the laboratory abnormalities that occurred in in at least 25% of patients treated with tagraxofusp-erzs in the safety population. The most common (incidence ≥ 10%) Grade ≥ 3 laboratory abnormalities were platelets decreased, hemoglobin decreased, neutrophils decreased, glucose increased, ALT increased and AST increased.

Safety Population - Common Laboratory Abnormalities

	N=94	
	All Grades %	**Grade ≥ 3 %**
Hematology		
Platelets decrease	67	53
Hemoglobin decrease	60	35
Neutrophils decrease	37	31
Chemistry		
Glucose increase	87	20
ALT increase	82	30
AST increase	79	37
Albumin decrease	77	0
Calcium decrease	57	2
Sodium decrease	50	9
Potassium decrease	39	4
Phosphate decrease	29	11
Creatinine increase	27	0
Alkaline phosphatase increase	26	1

Source: Dr. Jen's Section 8.5

Safety in Special Populations

Safety of tagraxofusp-erzs was described in three pediatric patients ages 10, 12, and 15 years. Two patients had relapsed/refractory BPDCN and one had newly-diagnosed BPDCN. They had received 2-5 cycles of tagraxofusp-erzs 12 µg/kg/day x 5 days. There was one Grade ≥ 3 adverse reaction (febrile neutropenia) reported. Overall, the safety profile in the children was similar to that reported in adults.

In the Safety Population, the incidence of encephalopathy (grouped term) was substantially higher in patients > 75 years old than in younger patients (45% vs 6%). The Clinical Reviewer could not confirm that this difference was not due to age alone and independent of treatment with tagraxofusp-erzs but recommended that its significance warranted description in labeling.

8.4 Safety Conclusions

The Clinical Reviewer concluded that the level of toxicity observed with the recommended dose and schedule of tagraxofusp-erzs is acceptable for the clinical benefit observed and recommended approval with special labeling as described above to mitigate risks.

Although persistent cytopenias were not observed in the clinical trials of tagraxofusp-erzs, there remains residual concern regarding the 68% incidence of treatment-emergent anti-IL-3 antibodies (see Section 5.3 for discussion). Although the redundancy in the hematopoietic cytokines may be sufficient to support hematopoiesis in homeostatic conditions if IL-3 is neutralized, the effect of such antibodies on hematopoietic recovery under a stressed condition, such as after hematopoietic stem cell transplantation, is not clear. Given the rarity of the disease, enhanced pharmacovigilance for reports of graft failure or delayed engraftment would be the most efficient method to ascertain additional data to address this concern.

9. Advisory Committee Meeting

This application was not discussed by an Advisory Committee.

10. Pediatrics

Tagraxofusp-erzs has orphan designation for treatment of blastic plasmacytoid dendritic cell neoplasm, and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). The available safety data in children was deemed sufficient to demonstrate safety in children and adolescents, and efficacy can be extrapolated from the adult study. These support approval for an intended population down to 2 years old.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations inspected four clinical sites (Sites, 2, 5, 6 and 9) and the Applicant for Study STML- 401-0114. The clinical sites chosen for inspection had the highest enrollment-weighted treatment effects or high rates of deaths and protocol violations. All inspections were classified as No Action Indicated (NAI). The study data from these clinical sites, were considered reliable in support of the requested indication.

12. Labeling

12.1 Prescribing Information

Summary of Significant Labeling Changes	
Section	**Recommended Labeling**
1	Extend intended population to pediatric patients 2 years and older.
2	Add instructions for management of CLS
5	Correct the incidence of CLS to include those with signs and symptoms of CLS (b) (4)
6	Expand safety population to all patients (n=94) active myeloid malignancies treated with the recommended dose and schedule of tagraxofusp-erzs. Add a table of laboratory abnormalities.
8	Add more detailed information about the pediatric and geriatric experience.
12	(b) (4)
13	(b) (4)
14	Reorganize information by indication (b) (4)

Summary of Significant Labeling Changes	
Section	**Recommended Labeling**
17	Add contraception counseling information

13. Postmarketing Recommendations

13.1 Risk Evaluation and Management Strategies (REMS)

Review determined that a REMS is not necessary to ensure that the benefits of tagraxofusp-erzs outweigh its risks. Labeling, including a Boxed Warning, and Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with tagraxofusp-erzs.

13.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMC-1
Perform a study to evaluate the impact of the removal of (b) (4) . If the data support removal of (b) (4) a plan for the removal of (b) (4) from the tagraxofusp-erzs manufacturing process will be provided. The plan should include an evaluation of consistency of the (b) (4) process and comparability of tagraxofusp-erzs manufactured with and without (b) (4) The final study report will be submitted in accordance with 21 CFR 601.12.

PMC-2
Conduct (b) (4) bioburden and endotoxin test method qualification using two additional drug substance batches. The final qualification report will be submitted in accordance with 21 CFR 601.12.

PMC-3
Perform a drug substance and drug product shipping study using the proposed commercial shipping lanes and modes of transportation to evaluate the impact of shipping on product quality. The study conditions should represent the worst case for tagraxofusp-erzs shipping and should evaluate product quality post-shipment using validated methods with pre-defined acceptance criteria. The shipping qualification report will be submitted in accordance with 21 CFR 601.12.

PMC-4
Conduct (b) (4) bioburden test method qualification using one additional batch of tagraxofusp-erzs drug product. The qualification report will be submitted in accordance with 21 CFR 601.12.

PMC-5
(b) (4) sterile filtration of tagraxofusp-erzs drug product (b) (4) The qualification report will be submitted in accordance with 21 CFR 601.12.

14. Appendices

Appendix 14.1: Listing of Clinical Trials Relevant to This BLA

Trial Name	Trial Design	Population	Primary Endpoint
STML-401-0114 Stage 1	Single-arm, open-label, multicenter	Adults ≥ 18 years old with R/R BPDCN (9) or AML (14) • N = 23 • Dose – 7-16 µg/kg/day x 5 days • Cycle length – 21 days	CR/CRc
STML-401-0114 Stage 2	Single-arm, open-label, multicenter	Adults ≥ 18 years old with R/R BPDCN (23) or AML (35) • N = 58 • Dose – 12 µg/kg/day x 5 days • Cycle length – 21 days	CR/CRc
STML-401-0114 Pivotal Cohort Stage 3	Single-arm, open-label, multicenter	Adults ≥ 18 years old with newly-diagnosed BPDCN • N = 13 • Dose – 12 µg/kg/day x 5 days • Cycle length – 21 days	CR/CRc
STML-401-0114 Stage 4	Single-arm, open-label, multicenter	Adults ≥ 18 years old with R/R BPDCN • N = 16 • Dose – 12 µg/kg/day x 5 days • Cycle length – 21 days	CR/CRc
STML-401-0214	Single-arm, open-label, multicenter	Adults ≥ 18 years old with adverse risk AML in CR1 or CR2 treated with tagraxofusp-erzs maintenance • N = 16 • Dose – 7, 9, or 12 µg/kg/day x 5 days • Cycle length – 28 days	
STML-401-0314	Single-arm, open-label, multicenter	Adults ≥ 18 years old with advanced, high risk MPN • N = 29 • Dose – 7, 9, or 12 µg/kg/day x 3 days • Cycle length – Cycles 1-4: 21 days, Cycles 5-7: 28 days, Cycles 8+ - 42 days	
STML-401-0414	Single-arm, open-label, multicenter	Adults ≥ 18 years old with R/R multiple myeloma treated with tagraxofusp-erzs in combination with pomalidomide and dexamethasone • N = 7 • Dose – 7 µg/kg/day x 5 days • Cycle length – 28 days	

Source: Dr. Jen's Table 1

15. Division Director

I concur with the recommendation for approval of tagraxofusp-erzs for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older. This approval is based on results from several single agent treatment cohort patient populations (newly diagnosed and relapsed refractory). No drugs are approved for treatment of BPDCN. The median overall survival is short. Patients who are newly diagnosed are usually treated with an intensive multiagent acute leukemia regimen followed by allogeneic stem cell transplantation in first remission. As noted above the results demonstrated a response rate where the lower 95% bound of the CR+CRc rate in the pivotal cohort with newly-diagnosed BPDCN exceeded 10% with a point estimate of 54%. The major identified safety issues were capillary leak syndrome, hypersensitivity, hepatoxicity, nausea, fatigue, peripheral edema, pyrexia, weight increase, and headache. Treating hematologists and oncologists should be able to manage these adverse reactions.

Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)

16. Office Director

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of tagraxofusp-erzs was also assessed by Drs. Przepiorka and Jen, and I concur with their recommendation to approve this biologic. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products (OHOP)

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/

DONNA PRZEPIORKA
12/21/2018

ANN T FARRELL
12/21/2018

RICHARD PAZDUR
12/21/2018