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APPLICATION NUMBER:

761116Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Emily Jen
BLA 761116
Elzonris (tagraxofusp-erzs)

CLINICAL REVIEW

Application Type	Original 351(a)
Application Number(s)	BLA 761116
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Division/Office	DHP
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Review Completion Date	11/21/18
Proper Name	tagraxofusp-erzs
(Proposed) Trade Name	Elzonris
Applicant	Stemline
Dosage Form(s)	1 mg in 1 mL single vial
Applicant Proposed Dosing Regimen(s)	12 µg/kg/day IV over 15 minutes on days 1-5 of a 21-day cycle
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	For the treatment of blastic plasmacytoid dendritic cell neoplasm in adults and pediatric patients 2 years and older

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Glossary

AC	advisory committee
AE	adverse event
AML	acute myeloid leukemia
BLA	biologics license application
BPDCN	blastic plasmacytoid dendritic cell neoplasm
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLS	capillary leak syndrome
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRS	cytokine release syndrome
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETA	individual residual for between subject variability
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRR	infusion-related reaction
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

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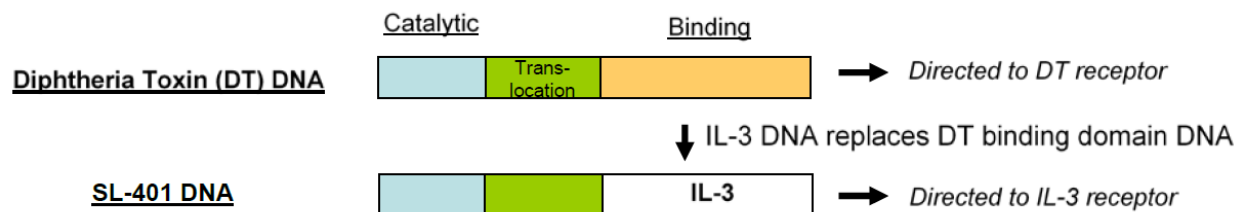
MM	multiple myeloma
MPN	myeloproliferative neoplasm
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Stemline submitted BLA 761116 for tagraxofusp-erzs (Elzonris®), also known as SL-401, a new molecular entity (NME) for the treatment of patients with blastic plasmacytoid dendritic cell neoplasms (BPDCN). Tagraxofusp-erzs is an immunotoxin conjugate comprised of recombinant human IL-3 fused to a truncated diphtheria toxin (DT) (Figure 1). The IL-3 domain targets cells that express IL-3R, including BPDCN tumor cells, and ultimately inactivates cellular protein synthesis leading to apoptosis.

Figure 1. Structure of Tagraxofusp-erzs (SL-401)



Source: STML-401-0114 Protocol page 32

The applicant's proposed indication is "for the treatment of patients with BPDCN." The proposed dose and schedule is 12 µg/kg/day IV over 15 minutes on days 1-5 of a 21-day cycle administered for as long as the patient is deriving clinical benefit.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The information submitted by the Applicant provides substantial evidence for the effectiveness of tagraxofusp-erzs for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and pediatric patients 2 years and older and supports regular approval for this indication.

This recommendation is based on the composite complete remission (CR) and clinical complete remission (CRc) rate with durability in patients with BPDCN treated with tagraxofusp-erzs on the single-arm, Phase 2 trial STML-401-0114. Pediatric patients were not included in the study, but safety data were available from three pediatric patients (b) (4). There were no new safety findings in this population, and pediatric BPDCN expresses CD123. Therefore, based on the biological plausibility that the efficacy of this targeted agent could be extrapolated from adults, the indication was extended to include pediatric patients 2 years and up.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Tagraxofusp-erzs is a diphtheria toxin-based immunotoxin that targets CD123 on blastic plasmacytoid dendritic cell neoplasm (BPDCN) cells. The benefit-risk assessment supports regular approval of tagraxofusp-erzs for the treatment of BPDCN in adult and pediatric patients 2 years and older.

BPDCN is a hematologic malignancy with clinical characteristics of both leukemias and lymphomas. There are no therapies currently approved for the treatment of BPDCN. Although the present standard of care is intensive multiagent chemotherapy followed by hematopoietic stem cell transplantation, the results with this approach are often not durable. Furthermore, the demographics of the patient population mean that such treatment options may not be available to or tolerated by many patients with the disease.

The recommendation for the approval is based on the results of STML-401-0114, a multicohort, nonrandomized study in patients treated with tagraxofusp-erzs for BPDCN as front line or relapsed/refractory therapy and patients with R/R AML. The pivotal cohort included 13 patients not previously treated for BPDCN. The CR/CRc rate in the pivotal cohort 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). Two additional responses were seen in patients with relapsed/refractory BPDCN.

Treatment-related mortality was low (2%) among all patients treated on study STML-401-0114 at the proposed dose for labeling. Sixty-day mortality was 15% among all patients and 5% among the subset of patients with BPDCN. This compares favorably with the morbidity and mortality seen with intensive chemotherapy regimens. No prolonged hematologic toxicities were seen in subjects with BPDCN treated with tagraxofusp-erzs.

Capillary leak syndrome was the only fatal toxicity seen with tagraxofusp-erzs. However, the risks were moderated in part by close monitoring and early interventions including the administration of albumin infusions and diuretics. Transient hepatotoxicity was frequently seen with tagraxofusp-erzs administration but usually resolved without intervention or with temporary dose interruption. A boxed warning for CLS is warranted, and the management strategy for these toxicities is outlined in Section 2.2 of the proposed prescribing information. The toxicity profile of tagraxofusp-erzs was similar in patients ages 75 years and older with the exception of increased Grade 1 and 2 encephalopathy, most commonly reported as a confusional state. This observation will be described in the prescribing information. Safety data were available for 3 pediatric patients treated with the proposed labeled dose and schedule of tagraxofusp-erzs. No new safety signals were identified in the

pediatric population. Tagraxofusp-erzs is a targeted therapy, and pediatric BPDCN tumor cells express CD123. Pediatric BPDCN would be expected to respond similarly to treatment with tagraxofusp-erzs compared with adult BPDCN, so the indication is extended to include pediatric patients 2 years and older.

Across the development program 95% of evaluable patients had pre-existing anti-drug antibody (ADA) likely due to standard diphtheria vaccination in the United States, and 99% developed treatment-emergent ADA by the end of Cycle 2. By Cycle 3, exposure to drug was markedly decreased with many patients having measurements below the limit of quantification of the assay. The median time to CR/CRc in STML-401-0114 was within 2 cycles, in the absence of progressive disease treatment with tagraxofusp-erzs continued indefinitely. However, tagraxofusp-erzs has been shown to be highly potent with an $IC_{50} \approx 10$ fM, ($\sim 10^6$ times lower than the lowest level of quantification of the assay), and most of the clinical toxicity was observed within the first 2 cycles when drug exposure was higher. Therefore, the there is no strong rationale to restrict the duration of treatment.

Overall, with the above appropriate risk mitigation strategies in place, 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 rare, aggressive disease and is universally fatal without treatment. - BPDCN occurs in all age groups, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. BPDCN has also been reported in pediatric patients as young as 8 months old. - In adults, a majority of patients relapse within 9 months and overall survival is reported at 7-12 months.	BPDCN is a fatal disease and represents an unmet medical need.
Current	Currently, there are no approved therapies and	There is a need for effective therapies to treat BPDCN,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Treatment Options	standard of care for BPDCN involves intensive combination chemotherapy followed by bone marrow transplantation. Given the demographics of the patient population, such treatment options may not be tolerated by or available to many patients with BPDCN.	especially treatments with less toxicity than intensive multiagent chemotherapy which may not be tolerated by a majority of the patient population with BPDCN.
Benefit	- Study STML-401-0114 was a single-arm, open label, multicenter trial of tagraxofusp-erzs monotherapy as first line or subsequent therapy for BPDCN. - Front line therapy for BPDCN: CR/CRc was achieved by 7/13 subjects [54% (95% CI: 25, 81)] and median duration of CR/CRc was not reached with median follow-up of 11.5 months (95% CI: 8.8, 11.9). - Treatment of relapsed/refractory BPDCN: CR/CRc was achieved by 2/15 subjects. Durations of response were 1.7 and 40.5 months. - Median time to CR/CRc was 1.9 months for front line therapy and 2.1 months in subjects with relapse/refractory disease.	Tagraxofusp-erzs was active in the treatment of BPDCN with a median time to response within 2-3 cycles, and the responses appeared to be durable.
Risk and Risk Management	- Fatal toxicities occurred in 6/139 (4%) of patients with active disease treated tagraxofusp-erzs monotherapy, and in 2/94 (2%) of patients treated with the proposed labeled dose and schedule of tagraxofusp-erzs (Focused Safety Population). - Both fatal toxicities in the Focused Safety Population occurred in subjects with BPDCN and were due to capillary leak syndrome (CLS) related to tagraxofusp-	The overall safety profile of tagraxofusp-erzs is acceptable for patients with BPDCN. To minimize risk, tagraxofusp will be administered inpatient during the 1st cycle. The prescribing information will include a boxed warning for capillary leak syndrome, CLS management guidelines, and Section 5 will describe the signs and symptoms observed with CLS. Hepatotoxicity will be included under

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	erzs. • The overall incidence of CLS was 56% in the Focused Safety Population with 9% Grade ≥ 3/C. Most events occurred during Cycle 1. In general, toxicities were manageable with monitoring and early intervention. The first cycle of therapy was administered in the inpatient setting. • Common adverse reactions (>30%) included signs and symptoms of CLS, elevated transaminases, nausea, pyrexia, fatigue, thrombocytopenia, and neutropenia. • Most elevated transaminases resolved without intervention or with temporary interruption of tagraxofusp-erzs. • The incidence of encephalopathy (grouped term) was higher in patients ages 75 years and older (risk difference 40%). • Safety data were available for 3 pediatric patients ages 10, 12, and 15 years with BPDCN treated with tagraxofusp-erzs at the labeled dose and schedule. There were no new safety findings in this population. • Ninety-six percent (115/120) of evaluable patients across 4 studies had pre-existing anti-drug antibodies at baseline due to diphtheria vaccination, and 99% (107/108) developed treatment-emergent ADA by the end of Cycle 2. There was an inverse correlation between drug exposure and ADA levels on Cycle 1 Day 1, and exposure by Cycle 3 was markedly decreased	warnings and precautions, and guidelines for management will be provided. No conclusions can be drawn based on a single-arm trial on whether the increase in encephalopathy observed in patients ≥ 75 years old is expected based on age alone, or if this represents a drug-specific toxicity to which these patients were more sensitive. However, the risk difference was significant, and the observation should be described in the prescribing information. Tagraxofusp-erzs is a targeted therapy, and pediatric BPDCN also expresses CD123. There is no biological reason to expect that pediatric BPDCN would not respond similarly to tagraxofusp-erzs compared with adult BPDCN. There were no unique safety concerns in this population. Therefore, the indication should be extended to include pediatric patients 2 years and up with BPDCN. The rates of baseline ADA and subsequent development of treatment-emergent ADA are high. However, tagraxofusp-erzs has been shown to be highly potent with an $IC_{50} \approx 10$ fM, ($\sim 10^6$ times lower than the lowest level of quantification of the assay), and most of toxicity was seen within the first 2 cycles. Therefore, there is no strong rationale to restrict the duration of treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with most measurements falling below the lower limit of quantitation for the assay.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy derived from type 2 dendritic cells. Diagnostic criteria for BPDCN were not formalized until the WHO 2008 guidelines (Facchetti, 2008) making assessment of historical data difficult to interpret. The actual incidence of BPDCN is unknown, but it has been estimated to account for <1% of leukemias or lymphomas (Pagano, 2016). BPDCN is more common in older adults (median age at diagnosis – 67 years) but does also occur in children. In a recent literature review of 365 cases in 125 publications published by Kim, et al, 2017, the authors report a bimodal distribution age distribution with an earlier peak in incidence between 8- 15 years in addition to the peak incidence in adults reported previously. There is an approximately 3-fold male predominance in adults while the distribution between sexes is more evenly distributed among pediatric patients.

Clinically, the disease exhibits characteristics of both leukemias and lymphomas. Most commonly (90%), the disease manifests as an indolent cutaneous lesion followed by rapid leukemic dissemination (Suzuki, 2005). Other extramedullary sites such as the lymph nodes, spleen, liver, or other organs may also be involved. A minority of cases present with acute leukemia with systemic involvement, often with multiple concurrent skin nodules (Pagano, 2013) but cases have also been reported without skin involvement (Rauh, 2012). Diagnosis is based on morphologic criteria and expression of markers including CD123 (IL-3R alpha), CD4, and CD56. Prior to 2008, when CD123 expression was not commonly assessed, cases of BPDCN may have been classified as NK cell leukemia or lymphoma, or hematodermic neoplasm.

Despite the rather indolent initial clinical presentation, the course of the disease is highly aggressive. The median overall survival in adults diagnosed with BPDCN is approximately 7-14 months (Pagano, 2013, Feuillard, 2002, Kim, 2017).

2.2. Analysis of Current Treatment Options

There are currently no therapeutics approved for the treatment of patients with BPDCN and there is no agreed-upon standard of care (Riaz, 2014). For adults and children not treated previously for BPDCN, treatment with leukemia or lymphoma (ALL, AML, NHL) multiagent chemotherapy regimens are used followed by allogeneic stem cell transplantation, if possible, but there have been no prospective trials.

The largest study investigating treatment assessed the results of first line treatments used in France for 86 patients (Poret, 2015). The overall response rate was 56%. However, the criteria used to define response were not reported. The highest response rates were obtained with intensive ALL-like, AML-like, and NK/T-like therapies at 71%, 79%, and 63% respectively. For patients who attained CR with these therapies, the median duration of response was 9-10 months. The response rate for CHOP-like groups was 31% with a median duration of remission

of 8-14 months. In the Italian multicenter study (Pagano, 2013), a retrospective analysis of 43 adults, patients who received ALL/aggressive NHL-like therapy (e.g. hyper-CVAD, CHOP) were more likely to achieve CR (based on AML criteria) than those treated with AML therapy. Median overall survival (OS) in this study was 9 months. Further review of the literature yields historical CR rates in adults ranging from 45-50% (Pagano, 2013; Poret, 2015; Pemmaraju, 2015; Dalle, 2010) but the response criteria used in these reports was not well defined. The reported median relapse-free survival (RFS) was 5-9 months. Median OS was 7-14 months from time of diagnosis with older patients on the lower end of the survival range.

The use of allogeneic stem cell transplantation (SCT) to sustain remission was described in the retrospective analysis from the European Group for Blood and Bone Marrow Transplantation (Roos-Weil, 2013) where 34 patients (median age 41) received allogeneic SCT after chemotherapy. Fifty-six percent were in first remission (CR1), and 44% were > CR1 or refractory. Three-year disease-free survival (DFS) was 33% and OS was 41%. For the subset who received myeloablative conditioning (median age 36) in CR1, 3-year DFS and OS were 45% and 60%, respectively. Only a single patient survived disease free after reduced intensity conditioning. Thus, allogeneic stem cell transplantation can result in longer DFS and OS, but it is mostly reserved for younger patients in CR1 with good performance status. Many patients with BPDCN are older or have multiple comorbidities and therefore may not be eligible for transplantation.

As noted above, the literature review by Kim, et al. 2017 showed a bimodal age distribution for BPDCN including a peak in the pediatric age group. The review included reports of 75 pediatric patients with BPDCN and noted that pediatric patients had more favorable outcomes than their adult counterparts. The remission rates with ALL, AML, and lymphoma-type regimens were 93%, 77%, and 80%, respectively. The overall “mean time to death/relapse” was reported as 12 months (± 15). A retrospective analysis of 29 children from the National Cancer Institute (Jegalian, 2010) (including 20 cases published in the literature) reported OS and EFS rates of 72% and 64% respectively with a median follow-up of 30 months (range: 9 months – 13 years). In general, the prognosis for pediatric patients is superior to adults, as they are better able to tolerate the intensive treatment regimens.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tagraxofusp-erzs is not marketed currently in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

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The trials included in this application were conducted under IND 114513.

List of Key Regulatory Interactions

- 3/26/12 – pIND meeting (TCON)
- 6/6/13 – Tagraxofusp-erzs was granted orphan drug designation for the treatment of BPDCN
- 6/27/14 – the IND was formally submitted
- 12/16/14 – Type C Guidance meeting to discuss the design of STML-401-0114 during which FDA noted that CR should be the primary efficacy endpoint and duration of response and overall survival should be key secondary efficacy endpoints
- 8/22/16 – Breakthrough Therapy Designation granted based on 7/12 (58%) CR in patients with BPDCN treated with tagraxofusp-erzs as frontline therapy
- 11/22/16 – CMC development program meeting
- 12/20/16 – Type B Breakthrough Therapy Developmental meeting to discuss the need for and design of a pivotal cohort that would include further safety monitoring for visual acuity impairment and follow-up for veno-occlusive disease after transplantation. FDA reiterated that CR should be the primary efficacy endpoint. FDA agreed that 5 patients enrolled after the cut-off date for the efficacy analysis presented at the meeting could be included in the Stage 3 pivotal cohort.
- 6/12/17 – WRO regarding proposed immunogenicity assays
- 8/16/17 – Type B CMC meeting
- 9/27/17 – Type B Multidisciplinary Guidance meeting – FDA (b) (4)
(b) (4) reiterated that CR with durability was the only accepted endpoint for regular approval. FDA agreed to review analyses in an independent data set to identify alternative criteria.
- 11/14/17 – Type A meeting to discuss results of analyse (b) (4)
(b) (4) FDA agreed that CR + CRc with durability was acceptable for demonstrating clinical benefit.
- 2/6/18 – Type B Multidisciplinary pBLA meeting
- 3/3/18 – Rolling review granted
- 4/5/18 – Part 1 submitted
- 6/21/18 – Part 3 submitted

3.3. Foreign Regulatory Actions and Marketing History

Tagraxofusp-erzs is not currently available in any foreign markets.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical

Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

There were nine study centers in the US, and 7/9 sites had enrolled patients at the time of the data cut-off. Inspections were requested for 4 sites; sites were chosen because they had the highest enrollment-weighted treatment effects, higher rates of deaths and protocol violations, or were outliers with respect to efficacy. An inspection of the sponsor records and study conduct was also requested. Inspections were conducted in April-June 2018 and all sites were classified by OSI as NAI (no deviation from regulations). This review can be found in DARRTS – CONSULT REV-DSI-02 dated June 11, 2018.

4.2. Product Quality

During the clinical development of tagraxofusp, (b) (4)

All protocols included in this submission used the liquid solution which is the only form intended for marketing at this time. Release data from process performance qualification lots are comparable to the clinical lots, and no product quality concerns were identified on preliminary CMC review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

One-month and three-month toxicology studies were performed in cynomolgus monkeys. Lethal doses were 60 µg/kg/day and 45 µg/kg/day, respectively, with death being secondary to severe necrosis of renal cortical tubules or undetermined. The main toxicities noted between the two studies were decreased appetite and body weight loss, hematologic toxicities, prolonged coagulation times, inflammatory response (increased neutrophils, globulin, and fibrinogen), liver toxicity (increases in ALT and AST, liver weights, hepatocellular vacuolation), kidney toxicity (increased BUN and creatinine; decreased albumin, phosphorus, and calcium; proteinuria; tubular degeneration/ necrosis). Renal and hepatic findings were reversible over a three-week recovery period in the 1-month study. Increased lung weights during the recovery period were observed in the 1-month study and mild lung edema was observed in the female with early mortality in the 1-month study and in one low dose male in the 3-month study.

No genetic toxicology, carcinogenicity, or reproductive and developmental toxicology studies were submitted. Based on its mechanism of action, tagraxofusp-erzs is expected to cause maternal and embryo-fetal toxicity when administered to pregnant women.

4.5. Clinical Pharmacology

There is a significant impact of both pre-existing and treatment-emergent tagraxofusp-erzs anti-drug antibodies (ADA) on PK exposure. During the clinical pharmacology review, it was noted that exposure on Cycle 1 Day 1 was inversely correlated with ADA titer at baseline (Figure 2). Among patients treated with tagraxofusp-erzs across 4 trials who were evaluable for the presence of pre-existing ADA, 96% (115/120) were confirmed positive at baseline. The high prevalence of ADA at baseline was likely due to standard administration of the diphtheria vaccine in the United States.

Ninety-nine percent (107/108) of evaluable subjects also had treatment-emergent ADA, with most patients showing an increase in ADA titer by the end of Cycle 2. Exposure in Cycle 3 was markedly decreased relative to Cycle 1, and many measurements were below the quantification limit of the assay. In STML-401-0114, the median time to response was around 2 cycles (see Section 7.1), but in the absence of disease progression treatment continued indefinitely.

Figure 2. Tagraxofusp-erzs Anti-Drug Antibody Effect on AUC

AUC_{0-last}, 12 µg/kg

ADA Titer	Cycle 1 Day 1			Cycle 3 Day 1		
	N	Mean	SD	N	Mean	SD
Not Detected	5	183	130	1	0.246	--
8	3	208	109	--	--	--
80	12	162	57.3	--	--	--
800	37	66.6	69.7	1	6.14	--
8,000	16	32.9	57.4	2	0	--
80,000	3	3.96	2.84	9	1.71	2.64
800,000	--	--	--	16	1.11	2.3
8,000,000	--	--	--	2	0	--

Source: FDA OCP Midcycle Meeting

However, tagraxofusp-erzs has been shown to be highly potent both *in vitro* and *in vivo* with an IC₅₀ ≈ 10 fM. This is approximately 1,000,000 times lower than the lowest level of quantification of the assay. Most of the clinical toxicity was seen within the first 2 cycles (see Section 8.5.1). Therefore, there is no strong rationale to restrict the duration of treatment.

4.6. Devices and Companion Diagnostic Issues

There was no companion device or diagnostic included in this application.

4.7. Consumer Study Reviews

There were no consumer study reviews for this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1. Table of Clinical Studies

Trial Name	Trial Design	Population	Primary Endpoint
Studies Supporting the Indication			
STML-401-0114 Pivotal Cohort Stage 3	Single-arm, open-label, multicenter, Phase 2	Adults ≥ 18 years old not previously treated for BPDCN - N = 13 - Dose – 12 µg/kg/day x 5 days - Cycle length – 21 days	CR/CRC
STML-401-0114 Stages 1, 2, and 4	Single-arm, open-label, multicenter, Phase 2	Adults ≥ 18 years old with R/R BPDCN - N = 15 - Dose – 12 µg/kg/day x 5 days - Cycle length – 21 days	CR/CRC
Studies Supporting Efficacy and Safety			
STML-401-0114 Stages 1, 2, and 4	Single-arm, open-label, multicenter, Phase 2	Adults ≥ 18 years old not previously treated for BPDCN - N = 16 - Dose – 12 µg/kg/day x 5 days - Cycle length – 21 days	CR/CRC
Studies Supporting Safety			
STML-401-0114 Stages 1, 2, and 4	Single-arm, open-label, multicenter, Phase 2	Adults ≥ 18 years old with BPDCN (any treatment status) or R/R AML - N = 17 - Dose – 7, 9, 12, or 16 µg/kg/day x 5	

		days
		• Cycle length – 21 days
*STML-401-0314	Single-arm, open-label, multicenter, Phase 2	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, Phase 2	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
^STML-401-0214	Single-arm, open-label, multicenter, Phase 2	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

*Not part of focused safety analyses (b) (4)

^Not part of pooled safety analyses; discussed separately in 8.9.5

5.2. Review Strategy

The FDA review was based on data from:

- BLA 761116
- Relevant published literature

The review of efficacy was based primarily on analyses of the pivotal cohort (Stage 3) of STML-401-0114 in patients not treated previously for BPDCN. Efficacy was also analyzed in patients with relapsed/refractory BPDCN treated in Stages 1, 2, and 4 of STML-401-0114. Efficacy was supported by analysis of patients not treated previously for BPDCN enrolled in Stages 1 and 2. These data were analyzed previously to support the composite CR/CRc endpoint.

The review of safety was based primarily on analyses of all patients treated on STML-401-0114. Subjects treated on STML-401-0314 were included in the full safety population overviews but were excluded from the focused safety population due to the different treatment schedule.

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All major efficacy and safety analyses were reproduced or audited. Summaries of data and statistical analyses by the reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and Excel 2016 (Microsoft, Redmond, WA). MedDRA Adverse Events Diagnostic 1.8 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. See the statistician's review for analyses of efficacy endpoints.

Table 2. BLA Submission and Amendments

SDN	eCTD SDN	Received	Category	Subcategory
1	1	4/4/18	Original	BLA – Rolling Submission Part 1 – BIMO data package
4	4	6/21/18	Original	BLA – Rolling Submission Part 3 – Clinical
3	3	4/13/18	Clinical	Response to Information Request
5	5	7/11/18	Clinical	Response to Information Request
7	7	7/17/18	Clinical	Response to Information Request
9	9	8/8/18	Clinical	Response to Information Request
10	10	8/13/18	Clinical	Response to Information Request
11	11	8/17/18	Clinical	Response to Information Request
16	16	9/17/18	Clinical	Response to Information Request
18	18	10/1/18	Clinical	Response to Information Request
20	20	10/23/18	Clinical	Response to Information Request
23	22	11/1/18	Clinical	Response to Information Request
25	25	11/8/18	Clinical	Response to Information Request
		11/19/18		Communication received by email regarding CLS in the PI

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. STML-401-0114

SL-401 in Patients with Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

6.1.1. Study Design

Overview and Objective

STML-401-0114 is a multicenter, open-label, multistage Phase 2 trial evaluating the safety and efficacy of tagraxofusp-erzs monotherapy in subjects with BPDCN or R/R AML.

- Stage 1 – dose escalation
 - Subjects with any BPDCN and R/R AML
 - Primary objective – to determine the maximum tolerated dose (MTD).
- Stage 2 - dose expansion
 - Subjects with any BPDCN and R/R AML
 - Primary objective – to determine the efficacy in subjects with BPDCN as assessed by ORR and to characterize the safety profile.
- Stage 3 – pivotal cohort supporting BLA
 - Subjects not treated previously for BPDCN
 - Primary objective – to determine the CR + CRc rate and characterize the safety profile in this population.
- Stage 4 – expanded access cohort
 - All subjects with BPDCN
 - Only stage of the study that remains open.

Key secondary objectives included determining the duration of response, PFS, and OS in subjects with BPDCN (pooled) as well as characterizing the pharmacokinetics and immunogenicity of tagraxofusp-erzs.

Trial Design

In Stage 1, doses of 7, 9, and 12 µg/kg/day x 5 days of a 21-day cycle were studied in subjects with BPDCN and R/R AML in a standard 3+3 dose escalation design. Doses up to 16 µg/kg/day x 5 days were studied only in subjects with R/R AML. The MTD for both populations was determined to be 12 µg/kg/day, and this was the dose was used in Stages 2-4.

Key eligibility criteria for the BPDCN population:

- Histological and/or cytological evidence of BPDCN by pathologic assessment at the investigative site according to WHO classification by a pathologist with expertise in hematologic malignancies, that can be measured for treatment response and is either:
 - Previously untreated (i.e., first-line) (Protocol Stages 2-4)
 - Persistent or recurrent in the peripheral blood, bone marrow, spleen, lymph nodes, skin, or other sites after previous treatment with at least 1 line of systemic therapy for BPDCN, e.g., stem cell transplantation or chemotherapy (Protocol Stages 1, 2, and 4).
- A pathology specimen must be available for central pathology review for all BPDCN subjects enrolled in Protocol Stages 2-4.
- Age ≥ 18 years
- ECOG performance status 0-2
- Adequate baseline organ function including:

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- LVEF $\geq$ institutional lower limit of normal as measured by multigated acquisition (MUGA) scan or 2-dimensional (2-D) echocardiography (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG)
 - Serum creatinine ≤ 1.5 mg/dL (133 μ mol/L)
 - Serum albumin ≥ 3.2 g/dL (32 g/L) (albumin infusions not permitted to enable eligibility)
 - Bilirubin ≤ 1.5 mg/dL (26 μ mol/L)
 - AST and ALT ≤ 2.5 times the upper limit of normal (ULN)
- Negative serum or urine pregnancy test within 1 week prior to treatment
- Acceptable contraceptive methods

Key exclusion criteria:

- Persistent clinically significant toxicities Grade ≥ 2 from previous chemotherapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]).
- Treatment with chemotherapy, wide-field radiation, or biologic therapy or another investigational agent within 14 days of study entry.
- Active malignancy and/or cancer history (excluding AML, BPDCN, or antecedent MDS) that may confound the assessment of the study endpoints
 - Eligible malignancies: non-melanoma skin cancer, carcinoma in situ, cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
- Cardiovascular disease – uncontrolled/any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
- Uncontrolled, clinically significant pulmonary disease (e.g., COPD, pulmonary hypertension)
- Receiving immunosuppressive therapy – with the exception of low-dose prednisone (≤ 10 mg/day) – for treatment or prophylaxis of graft-versus-host disease (GVHD).
 - If the patient has been on immunosuppressive treatment or prophylaxis for GVHD, the treatment(s) must have been discontinued at least 14 days prior to study treatment and there must be no evidence of Grade ≥ 2 GVHD.
- Pregnant or breast feeding.
- HIV-positive or active/chronic Hepatitis B or C
- Oxygen-dependent

Treatment Plan

12 μ g/kg/day IV infusion over 15 minutes for 5 consecutive days of a 21-day cycle – treatment may continue indefinitely provided the patient is deriving benefit.

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- First cycle must be administered in the inpatient setting with hospitalization beginning the day of the 1st infusion (or prior day) and ending 24 hours after the last infusion
- Subsequent cycles may be administered in an outpatient ambulatory care setting equipped for intensive monitoring. Subjects must be monitored for at least 4 hours following each infusion.

Premedication:

- Acetaminophen 650 mg (or equivalent dose of paracetamol) orally (PO)
- Diphenhydramine 50 mg intravenously (IV) (or equivalent dose of another H1-histamine antagonist)
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Ranitidine 50 mg IV (or an equivalent dosage of another H2-histamine antagonist)

Monitoring during the dosing period (Days 1-5 of a cycle) and Days 8, 15, and 21:

- Vital signs – BP, HR, RR, temperature and pulse oximetry immediately prior to and immediately after completion of infusion and 30, 60, and 240 minutes post-infusion
- Daily CBC, CMP, total protein, uric acid, coagulation labs

Dose Modifications

- Infusions may be delayed to allow for toxicity resolution. If dosing is resumed within a cycle, any subsequent doses must be given within the 1st 10 days of the cycle; subjects may receive fewer than 5 doses.
- Tagraxofusp-erzs may be resumed at the same dose level or reduced a dose for Grade 3 or 4 toxicities.

CLS is associated with vascular endothelial injury related to fusion protein administration and may occur 3 – 8 days after initiation of treatment. Subjects may exhibit symptoms of hypotension, fluid overload, evidenced by weight gain or edema, nausea, and anorexia, shortness of breath and, at times, confusion and muscle injury. Findings may include hypoalbuminemia, reductions in blood oxygen saturation, and evidence of pulmonary edema on chest x-ray. These symptoms may present individually or as part of CLS.

Withhold tagraxofusp-erzs for:

- SBP $\leq$ 80 mmHg – treat with fluid bolus and hold drug until resolution; if hypotension persists such that further treatment is not feasible during the day of the intended dose and the following day, no further doses will be given in that cycle
- Body weight increase $\geq$ 1.5 kg over pre-treatment weight on the previous treatment day – may treat with fluid restrictions or diuretics (e.g. furosemide) as clinically indicated and should also receive albumin 25 g IV daily or every 12 hours until weight gain has resolved. Dosing within a cycle may resume only if $\geq$ 1.5 kg weight gain has resolved
- Hypoalbuminemia –

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- o Albumin 3.0-3.5 g/dL (30-35 g/L) or decreased by ≥ 0.5 g/dL (5 g/L) below the level at the start of the cycle – withhold SL-401 infusion and administer albumin 25 g IV daily or every 12 hours as clinically feasible until serum albumin is both ≥ 3.5 g/dL and not reduced by ≥ 0.5 g/dL from the level at the start of the cycle prior to resuming treatment with SL-401 in the same cycle.
 - o Albumin < 3.0 g/dL (30 g/L) or reduced by more than 1.0 g/dL (10 g/L) below the level at the start of the cycle (i.e., from 4.3 g/dL to 3.2 g/dL) – withhold SL-401 infusions for the duration of that particular cycle. Albumin should be administered until the albumin level is at least above 3.5g/dL. Consultation with the medical monitor is advised.
 - o Dosing in the next cycle may resume if albumin remains at 3.5 g/dL without additional albumin infusions.
- Capillary leak syndrome – withhold for clinical signs and symptoms consistent with CLS. If CLS is identified, 1 mg/kg/day of methylprednisolone (or equivalent) should be administered until resolution or as clinically indicated along with albumin
 - o Do not resume administration during a cycle if there are signs/symptoms of CLS with evidence of hemodynamic instability, significant clinical deterioration or changes in albumin (decrease to < 3.0 g/dL (30 g/L) or reduced by more than 1.0 g/dL (10 g/L) below the level at the start of the cycle) or CLS elements have not resolved.
 - o In the setting of signs/symptoms of CLS without evidence of hemodynamic instability OR clinical deterioration OR reductions in albumin that would prevent further dosing, tagraxofusp-erzs administration in the cycle may be delayed and resume if no evidence of ongoing CLS. Any subsequent dose should be administered on days subsequent to identification of the abnormality.
- Chills/ anaphylaxis/hypersensitivity reactions – withhold tagraxofusp-erzs.
 - o Chills may be treated with meperidine 12.5-50 mg IV or morphine sulphate 1-2 mg IV (or equivalent doses of other opiates).
 - o Anaphylaxis and hypersensitivity reactions associated with rash, fever, urticaria, bronchospasm, and/or angioedema will be treated with 100 mg IV methylprednisolone (or an equivalent corticosteroid) and 25-50 mg IV diphenhydramine (or equivalent H1-histamine antagonist). More severe symptoms will also be treated with 0.3 mL epinephrine (1:1000) IV once.
 - o Subjects with anaphylactic (Grade 4) reactions or Grade ≥ 3 hypersensitivity reactions should not receive additional doses.
- Transaminase elevation $> 5x$ ULN – no further doses in that cycle
- Temp $\geq 38C$ – draw blood culture x 2, collect urine for urinalysis – dose may be administered pending resolution of fever provided that appropriate evaluation for infectious etiologies has been undertaken (may resume on same day as temperature elevation or on subsequent days)

- Serum creatinine > 1.8 mg/dL – withhold until creatinine resolves to ≤ 1.8 mg/dL; dosing may resume upon recovery if within the 1st 10 days of the cycle
- HR ≥ 130 or ≤ 40 bpm or SBP ≥ 160 mmHg – hold until resolution
- “Clinically significant” Grade 3/4 toxicities for the current cycle except Grade 3: arthralgia, myalgia, fever responding to treatment without active infection, nausea//vomiting/diarrhea associated with suboptimal prophylaxis or treatment, reversible chemistry abnormalities except as above

Table 3. STML-401-0114 – Dose Modifications for Nonhematological Toxicities

CTCAE Grade	SL-401 Dose Adjustment/Delays
Any Grade 1-2 toxicities	• No dose adjustment or delay
Grade 3 with resolution to Grade ≤ 1 or baseline by Day 21 of cycle	• No dose adjustment or delay
Grade 3 without resolution to Grade ≤ 1 or baseline by Day 21 of cycle	• Delay the start subsequent cycle by up to 14 days (i.e., up to 35 days since the first dose in the previous cycle).
	– If after 14 days the toxicity resolves to Grade ≤ 1 or baseline, no dose adjustment required and the cycle may start. – If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor.
Grade 4 (excluding transient [≤ 14 days] asymptomatic transaminase or CPK elevations) with resolution to Grade ≤ 1 or baseline by Day 21 of cycle	• Reduce dose for subsequent cycle (see Section 7.5.5.11) and the cycle may start.
Grade 4 without resolution to Grade ≤ 1 or baseline by Day 21 of cycle	• Delay the start subsequent cycle by up to 14 days (i.e., up to 35 days since the first dose in the previous cycle). • If after 14 days the toxicity resolves to Grade ≤ 1 or baseline, resume dosing at a reduced dose (see Section 7.5.5.11). • If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor

Source: STML-401-0114 Protocol, Amendment 10, Table 4.

Hematological toxicity:

- Subjects with neutropenia or thrombocytopenia secondary to disease do not require treatment interruptions for myelosuppression. Dose-modifications in these subjects should be considered on a case-by-case basis and discussed with the Medical Monitor. The following guidelines can be used for these subjects:
- Subjects with a response and pre-cycle counts of neutrophils $>1000/\mu\text{L}$ and platelets $>50,000/\mu\text{L}$ with sustained low counts of neutrophils $<500/\mu\text{L}$ and/or platelets $<20,000/\mu\text{L}$ for > 2 consecutive weeks in the current cycle may receive a subsequent cycle at a reduced dose, at the Investigator's discretion.
- For persistent circulating blasts or $>5\%$ blasts in the bone marrow, continue treatment regardless of neutrophil and platelet count and give supportive care as needed.
- If no evidence of leukemia in the bone marrow, consider holding (postponing) therapy until recovery of neutrophils to $\geq 1000/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, then resume tagraxofusp-erzs at the same or reduced dose according to guidelines mentioned above.

Table 4. STML-401-0114 – Dose Reductions

Dose for a Given Cycle	Reduced Dose for Subsequent Cycle
12 $\mu\text{g/kg/day}$	9 $\mu\text{g/kg/day}$
9 $\mu\text{g/kg/day}$	7 $\mu\text{g/kg/day}$
7 $\mu\text{g/kg/day}$	5 $\mu\text{g/kg/day}$

Source: STML-401-0114 Protocol, Amendment 10, Table 5.

Tumor response assessments:

- All – Screening, end of Cycle 1 and 2
- Marrow – in subjects with marrow involvement prior to study treated, further evaluations will be done following Cycles 4 and 6, then every 3 months from months 6-12; every 6 months from months 12-24; every 12 months thereafter
- Skin – photographs and mSWAT at the start of every 2nd cycle after Cycle 2
 - “A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist”
- CT – after start of Cycles 2, 4, 6, and 21 days after the start of every 4th cycle thereafter

Criteria for Discontinuation:

- Patient withdrawal of consent
- Occurrence of unacceptable toxicity, including DLT

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- SL-401 related anaphylaxis or Grade ≥ 3 hypersensitivity reaction
- Requirement for >1 dose reduction unless there is evidence of response (beyond Cycle 1), in which case additional dose reductions are permitted, however these reductions must be discussed with the Medical Monitor and documented in the context of ongoing response
- Disease recurrence/progression
- Intercurrent illness that prevents further administration of SL-401
- Patient non-compliance
- Occurrence of pregnancy
- Investigator's decision

Recommended prophylactic therapies/regimens per institutional guidelines/practices:

- Antibacterial: ciprofloxacin, levofloxacin, or an equivalent antibiotic
- Antifungal: fluconazole, voriconazole, or an equivalent antifungal

Allowed medications:

- Supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures.
- Subjects may receive growth factor support and/or blood product transfusions as per the discretion of their physician.
- Albumin 25 g IV daily should be administered if serum albumin is between 3.0-3.5 g/dL (30-35g/L) on days that dosing occurs or if it is <3.0 g/dL (30 g/L) on days when treatment has been withheld or in the immediate post-treatment period.

Study Endpoints

Disease Response in BPDCN

The primary endpoint was complete remission (CR) + CR [clinical] with minimal residual skin abnormality (CRc) (Table X).

Response/remission were assessed using International Working Group (IWG) criteria for AML (for subjects with AML or BPDCN) (Cheson, 2003), a modified version of the Revised Response Criteria for Malignant Lymphoma (for subjects with BPDCN) (Cheson, 2007), and weighted BSA/modified Severity Weighted Assessment tool (mSWAT) score (Olsen, 2011).

Assessment of response and disease progression included evaluation of all sites of disease involvement at baseline, including skin, lymph nodes, spleen, liver, peripheral blood, and bone marrow. Up to 6 of the largest dominant nodes or nodal masses were identified as index lesions for radiographic response assessments.

Table 5. STML-401-0114 – Tumor Response Criteria for Subjects with BPDCN

Response	Location	Criteria
Complete Response (CR)	Marrow ^b	• Normalization of blast percentage ($\leq 5\%$) ^b
	Peripheral Blood	• Normalization of neutrophil count ($\geq 1,000/\mu\text{L}$) and platelet count ($\geq 100,000/\mu\text{L}$) • Absence of leukemic blasts
	Skin ^a	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline ^a
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR with incomplete blood count recovery (CRi)	Marrow ^b	• Normalization of blast percentage ($\leq 5\%$) ^b
	Peripheral Blood	• Incomplete recovery of neutrophil and/or platelet count • Absence of leukemic blasts
	Skin ^a	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline ^a
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR [clinical] with minimal residual skin abnormality (CRc)	Marrow ^b	• Normalization of blast percentage ($\leq 5\%$) ^b
	Peripheral Blood	• Normalization of neutrophil count ($\geq 1,000/\mu\text{L}$) and platelet count ($\geq 100,000/\mu\text{L}$) • Absence of leukemic blasts
	Skin ^a	• Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed) ^a
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
Partial Response (PR)	Marrow ^b	• Decrease by $\geq 50\%$ in blast percentage to 5 – 25% ^b
	Peripheral Blood	• Normalization of neutrophil count ($\geq 1,000/\mu\text{L}$) and platelet count ($\geq 100,000/\mu\text{L}$)
	Skin ^a	• 50% – <100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline ^a
	Nodal Masses	• $\geq 50\%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes
	Spleen, Liver	• $\geq 50\%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen
Stable Disease (SD)		• Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks
Relapse after CR/CRi/CRc	Marrow ^b	• Blast percentage $> 5\%$ (if no peripheral blasts, then confirmation aspirate required ≥ 1 week later) ^b
	Peripheral Blood	• Presence of leukemic blasts
	Skin ^a	• Increase in skin score greater than the sum of nadir plus 50% baseline score ^a
	Nodal Masses	• Appearance of a new lesion(s) > 1.5 cm in any axis, $\geq 50\%$ increase from nadir in SPD of more than one node, or $\geq 50\%$ increase from nadir in longest diameter of a previously identified node > 1 cm in short axis
	Spleen, Liver	• $> 50\%$ increase from nadir in the SPD of any previous lesions

Source: STML-401-0114 Protocol Amendment 10, Appendix B.

The key secondary endpoint was Duration of CR/CRc. This was defined as the time from when measurement criteria are first met for CR/CRc (whichever recorded first) until the date that the criteria for relapse after CR/CRc was met. For subjects who received bone marrow transplantation after CR/CRc, duration of response included time to disease relapse post-transplantation. Subjects lost to follow-up or who did not relapse after CR/CRc as of the cut-off for analysis were censored at the date of last radiologic assessment while on study. Analysis of duration of response was performed by Kaplan-Meier time to event analysis to estimate the 25th percentile, median, and 75th percentile of times to event, number, and percentage of events, censored observations, and appropriate confidence intervals. Additional descriptive analysis will be performed separately for subjects who do and do not receive bone marrow transplantation.

Statistical Analysis Plan

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.

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.

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.

Table 6. STML-401-0114 – Protocol Amendment Summary

Amendment	Major Changes
Protocol Amendment 5 (28 Jul 2014)	• First version under which patient enrollment occurred
Protocol Amendment 6 (01 Dec 2014)	• Implemented during Stage 1 dose-escalation • Provided risk mitigation strategies for CLS • Modified eligibility criteria to require subjects to have normal LVEF prior to study entry • Increased monitoring during the infusion period • Required treatment delay (minimum 1 day) for early signs/symptoms consistent with CLS (weight gain, hypotension, decreased serum albumin) until evidence of stability

Protocol Amendment 7 (11 Aug 2015)	• Enrollment of Stage 2 BPDCN treated at 12 mcg/kg/day began with this amendment • Safety: - Required higher minimum albumin for eligibility - Required cessation of therapy within any study cycle if significant albumin reductions or Grade 3+ transaminase elevations - In the setting of early CLS or Grade 3 transaminase elevations, fewer than 5 doses could be administered in a cycle • Stage 1 cohorts expanded to include dose levels > 12 mcg/kg/day in AML subjects • Grade 3+ nonhematologic AEs unrelated to persistent leukemia were added to DLT definitions • IRC would assess response for BPDCN subjects • Quantification of skin disease burden via mSWAT required at time of each skin assessment
Protocol Amendment 8 (08 Feb 2016)	• Stage 1 complete with MTD of 12 mcg/kg/day identified in R/R AML • Entrance criteria revised to include subjects with previously untreated BPDCN • Study objectives for BPDCN in Stage 2 revised - Primary: ORR - Secondary: CR rate (including CRi and CRc), DOR, PFS, OS • Overall sample size increased from 60 up to 100 total subjects (BPDCN and R/R AML) with 30-40 subjects with BPDCN expected (no formal sample size calculation) • Positive sites of disease identified at screening were required to be followed during study at every response evaluation • Subjects would be followed for response and survival until assessment of primary and secondary objectives was complete for all subjects. • Maximum duration of 6 cycles eliminated
Protocol Amendment 9 (08 Feb 2017)	• Closed Stage 2 • Added Stage 3 as a standalone pivotal cohort of subjects with first-line BPDCN enrolled on or after 26 Oct 2016 until sufficient subjects were enrolled to ensure 10 subjects were included in the mITT analysis population • Primary endpoint – “CR rate” (CR + CRc)

	• Stage 4 added to continue enrolling subjects with R/R BPDCN or front-line subjects after Stage 3 completed enrolling • Total sample size increased to 270, including 70 BPDCN subjects • Safety monitoring updated to including monitoring and assessment of visual acuity and color vision and follow-up to determine whether treatment with tagraxofusp-erzs altered the risk of VOD after subsequent SCT
Protocol Amendment 10 (27 Mar 2018)	• Total sample size increased to 130 subjects including 80 with BPDCN to endure continued access • Updated guidance for toxicity management including CLS management • Primary efficacy endpoint updated to CR + CRc per agreement with FDA

Source: STML-401-0114 CSR

6.1.2. Study Results

Compliance with Good Clinical Practices

The protocol and clinical study report stated that the trial was conducted in compliance with Good Clinical Practice (GCP) and was reviewed by an institutional review board (IRB). A list of study sites and investigators for STML-401-0114 was also provided. Data monitoring was conducted by an independent clinical research organization (CRO) to ensure conduct of the trial according to GCP ICH guidelines. This trial was conducted only in the United States.

Four clinical sites and the applicant were audited for this application (see Section 4.1) and were classified as NAI (no deviation from regulations).

Financial Disclosure

The applicant submitted financial disclosure information from the principal investigators and subinvestigators from STML-401-0114. Two investigators (Sites (b) (6)) had disclosable financial interests in which the applicant paid the respective institutions under a financial agreement. In the first case, the Applicant had two agreements with (b) (6) (b) (6). In the second case (Site (b) (6)) the Applicant made a total of \$300,000 in grant payments to establish a (b) (6) (b) (6) to support “further research in BPDCN” and other cancers. The investigator manages this fund while he remains at (b) (6). Neither investigator received any direct payment and both sites were inspected. A sub-investigator at Site (b) (6) submitted a disclosure regarding discussions between Stemline and (b) (6).

(b) (6) However, at the time of submission, no agreement had been executed and no payments made. The applicant notes that in order to minimize the potential for bias, data-monitoring of the study was conducted by an independent CRO to ensure accurate implementation of protocol requirements across participating sites.

Reviewer comment: Both sites in question were inspected by OSI. Site (b) (6) enrolled (b) (6) subjects in the pivotal cohort with 1 CR and 1 CRc. Site (b) (6) enrolled (b) (6) subjects in the pivotal cohort and had a reported treatment effect of 0% CR/CRc. Confirmation of disease response was performed by an independent review committee, and these analyses are included in the submission. The first subject from Site (b) (6) had a response outside the time period reviewed by the independent reviewers whose last assessment at Day 30 was CRi. However, the subject does have subsequent documented count recovery within 5 days of a negative marrow. The second subject from Site (b) (6) had a CRc confirmed by both independent reviews on Day 38. Therefore, the financial conflicts of interest do not appear to have compromised the integrity of the trial data.

Data Quality and Integrity

In general, the data file quality for Study STML-401-0114 appeared to be acceptable for review.

FDA independently adjudicated first/best response and time to CR/CRc for all subjects based on the following data from ADRS: study day of marrow response, skin response, and lymph node or visceral response (if present at baseline). The bone marrow assessment closest in date to the extramedullary responses and count recovery (ANC and platelets from ADLB) within 14 days of that marrow were used. Time to CR/CRc was the earliest study day at which subjects met all parts of the definition detailed in Table 5. All analyses for the FDA efficacy review were performed using FDA’s adjudicated disease response and time to response.

For the 4 subjects described in Table 7, the FDA adjudicated assessment of overall response (ADRS – Overall Response AVALC and ADTTE – BESTRESP) differed from the Applicant’s reported response.

Table 7. STML-401-0114 – FDA Adjudication of Response

Patient SUBJID	Applicant *Overall Response and day of first CR/CRc	FDA Overall Response and day of first CR/CRc	Pertinent disease assessments
(b) (6)	CRc – Day 23	CRi – Day 23	• This patient never achieved platelets >100 x 10 ⁹ /L.
	CRi – Day 50	+CR – Day 50	• ANC recovery: Day 49

(b) (6)	CRi – Day 45	CR – Day 45	• Platelet recovery: Day 43 • Bone marrow CR: Day 50
	CRc – Day 25	CRi – Day 81	• Platelet recovery on Day 38 (Days 26-38). • This patient never had ANC recovery within 14 days of any marrow assessment and had an ANC > 1x10⁹/L only once between pre-treatment and the last CBC on Day 81. He does not meet the definition of CR. • Patient with baseline lymph node disease • 1st Lymph node CR: Day 81

Source: FDA Analysis

For the 10 subjects described in Table 8, the FDA adjudicated Time to CR/CRc differed from the Applicant's reported result.

Table 8. STML-401-0114 – FDA Adjudication of Time to Response

Patient SUBJID	Applicant *Overall Response and day of first CR/CRc	FDA Overall Response and day of first CR/CRc	Pertinent disease assessments
(b) (6)	CR – Day 22	CR – Day 57	• Patient with baseline lymph node disease • 1st Lymph node CR: Day 57
	CR – Day 128	CR – Day 131	• MSWAT: CR on Day 131
	CRc – Day 18	CRc – Day 81	• Patient with baseline visceral disease • 1st visceral CR: Day 81 • MSWAT Day 81: CRc
	CR – Day 17	CR – Day 82	• Patient with baseline lymph node disease • 1st Lymph node CR: Day 82
	CR – Day 92	CR – Day 107	• Patient with baseline lymph node disease • 1st Lymph node CR: Day 107
	CRc – Day 23	CRc – Day 43	• Patient with baseline lymph node disease • 1st Lymph node CR: Day 43
	CR – Day 52	CR – Day 32	• Bone marrow CR: Day 29 • ANC recovery: Day 32 • Platelet recovery: Day 24

(b) (6)	CR – Day 142	CR – Day 63	• No baseline skin/LN/visceral disease • Bone marrow CR: Day 52 • ANC recovery: Day 57 • Platelet recovery: Day 55 • 1st MSWAT CR: Day 63 • No baseline LN/visceral disease
	CRc – Day 44	CRc – Day 46	• ANC recovery: Day 46
	CR – Day 21	CR – Day 49	• Patient with baseline lymph node disease • 1st Lymph node CR: Day 49

Source: FDA Analysis

Patient Disposition

The first subject enrolled in Stage 1 started treatment on October 6, 2014.

In accordance with agreement with FDA in the Type B meeting on December 20, 2016, first-line BPDCN patients enrolled on or after October 26, 2016 were included in the pivotal cohort (Stage 3). The cutoff date for analysis of data for the primary efficacy analysis was September 25, 2017. All surviving patients enrolled into Stage 3 included in this data submission had completed at least 6 months of follow-up. Thirteen subjects were enrolled in the pivotal cohort (Stage 3). Overall, 32 subjects with no prior treatment for BPDCN were enrolled and 29 were treated at the dose intended for marketing.

Table 9. STML-401-0114 – Patient Disposition

	No prior treatment for BPDCN		Relapsed/Refractory BPDCN
	Pivotal Cohort (Stage 3)	Stages 1 and 2	
Received treatment	N = 13	N = 16	N = 15
Therapy ongoing	0	2 (13%)	0
Discontinued therapy	13 (100%)	14 (88%)	15 (100%)
Fatal adverse event	1 (8%)	0	0
HSCT			
• In CR/CRc	6 (46%)	6 (38%)	1 (6%)
• In PR	0	1 (6%)	0
Progressive primary disease	4 (31%)	6 (38%)	12 (80%)
Physician decision or patient withdrawal	3 (23%)	1 (6%)	2 (13%)

Source: FDA analysis

Clinical Review
Emily Jen
BLA 761116
Elzonris (tagraxofusp-erzs)

Protocol Violations/Deviations

There were no major protocol deviations that resulted in exclusion of subjects from any analyses.

Protocol violations involving the investigational product in the pivotal cohort included 6/13 subjects having at least one dose infusion duration extended to >20 minutes. No over- or under dosing was reported. Other violations included study procedures not done per protocol (pre-infusion EKG, translational samples not collected, CT/skin biopsy/mSWAT not done per protocol or not done correctly) or changes to the visit window.

Protocol violations involving the investigational product in the relapsed/refractory subjects included 6/15 subjects having at least one dose infusion duration extended to >20 minutes. No over- or underdosing was reported. One subject (b) (6) had “other anti-cancer agent initiated during study” on Day 56 but no details were provided. This subject was considered by both the Applicant and by FDA as a non-responder. Other violations included study procedures not done per protocol (doses not withheld for weight gain > 1.5 kg, T38C, SPB >= 160, pre-infusion EKGs and post-infusion vitals not done).

Patient Population

Table 10. STML-401-0114 – Demographics and Baseline Disease Characteristics

	No Prior Treatment for BPDCN			R/R BPDCN
	Pivotal Cohort (Stage 3) N = 13	Stages 1 and 2 N = 16	Pooled N = 29	Stages 1, 2, and 4 N = 15
Sex				
• M	11 (85%)	12 (75%)	23 (79%)	13 (87%)
• F	2 (15%)	4 (25%)	6 (21%)	2 (13%)
Age (years)	65	67.5	67	72
Range	22-84	28-84	22-84	44-80
Race				
• White	13 (100%)	14 (88%)	27 (93%)	13 (87%)
• American Indian	-	1 (6%)	1 (3.5%)	-
• Hispanic	-	1 (6%)	1 (3.5%)	-
• Asian	-	-	-	2 (13%)
ECOG				
• 0	8 (62%)	7 (44%)	15 (52%)	5 (33%)
• 1-2	5 (38%)	9 (56%)	14 (48%)	10 (67%)

Clinical Review
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Baseline organ involvement				
• Marrow blasts >5%	7 (54%)	7 (44%)	14 (48%)	9 (60%)
• >5 - <40% blasts (range)	3 (12-30)	5 (9-38)	8 (9-38)	4 (10-30)
• ≥40% blasts (range)	4 (60-94)	2 (64-80)	6 (60-94)	5 (40-84)
• Skin	13 (100%)	15 (93%)	28 (97%)	13 (87%)
• Lymph node	6 (46%)	7 (44%)	13 (45%)	8 (53%)
• Visceral	2 (15%)	2 (13%)	4 (14%)	4 (27%)
Time since diagnosis				
Months (median)	0.8	1.0	1.2	12
Range	0.0, 3.1	0.0, 10.4	0, 10.4	2.6, 84.4

Source: FDA Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In the pivotal cohort 62% of subjects received at least 80% of the planned doses in Cycle 1 and all subjects completed all doses of Cycle 2 onward. When pooled with the supportive cohort, 72% of subjects had at least 80% compliance in Cycle 1. In the relapse/refractory subjects, at least 80% of planned doses were administered in 40% of subjects in Cycle 1 and 73% in Cycle 2.

Table 11. STML-401-0114 – Treatment Compliance: Total Doses of Tagraxofusp-erzs Received per Cycle (Cycles 1-3)

	Front Line			Relapsed/ Refractory
	Pivotal Cohort (Stage 3)	Supportive Cohort (Stages 1 and 2)	Pooled	
Cycle 1	N = 13	N = 16	N = 29	N = 15
• 5	5 (38%)	7 (44%)	13 (45%)	8 (53%)
• 4	3 (23%)	5 (31%)	8 (28%)	1 (7%)
• 3	2 (15%)	3 (19%)	5 (17%)	5 (33%)
• 2	2 (15%)	1 (6%)	3 (10%)	1 (7%)
Cycle 2	N = 12	N = 16	N = 28	N = 13
• 5	12 (100%)	15 (94%)	27 (96%)	10 (77%)
• 4	0	1 (6%)	1 (4%)	1 (8%)
• 3	0	0	0	1 (8%)
• 2	0	0	0	0
• 1	0	0	0	1 (8%)
Cycle 3	N = 11	N = 16	N = 27	N = 9
• 5	11 (100%)	15 (94%)	26 (96%)	9 (100%)
• 1	0	1 (6%)	1 (4%)	0

Source: FDA Analysis

Clinical Review
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Elzonris (tagraxofusp-erzs)

In Cycle 4 onward, any subjects starting the cycle completed all 5 planned doses in the cycle with the exception of 1 subject each in Cycles 6 and 7 who discontinued due to disease progression, and 1 subject in Cycle 37 in whom a reason for discontinuation was not provided in the safety update.

Concomitant medications were recorded in the ADCM data set. The concomitant medications used most frequently in the pivotal cohort were oral antihypertensives, treatment for diabetes, drugs for functional gastrointestinal disorders, statins, and nutritional supplements.

Efficacy Results

See efficacy results in Section 7.1.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Cohorts

7.1.1. Primary Endpoints

Validation of CR/CRc as an Endpoint for BPDCN

In earlier amendments of the STML-401-0114 protocol, (b) (4)
(b) (4) FDA reiterated on several occasions that the acceptable endpoint for regulatory decision-making was complete remission (CR) only. However, FDA agreed to review analyses performed on an independent data set to identify alternative criteria.

On November 14, 2017 a meeting was held between FDA and the applicant to discuss data to support the primary endpoint for the pivotal cohort. In preparation for that meeting, the applicant submitted analyses of data (b) (4)

(b) (4)
(b) (4)
(b) (4)
Based on these data, FDA agreed that CR + CRc with durability was an acceptable criterion for demonstrating the clinical benefit of tagraxofusp-erzs in this population. Additionally, FDA requested that the applicant revise the definition of CRc to clarify the meaning of “marked clearance of all skin lesions” (see Table 5). The applicant defined marked clearance as “greater than 75% from baseline and less than 10% residual overall.”

STML-401-0114 – Primary Efficacy

FDA independently adjudicated response and Time to CR/CRc for all subjects as described in Section 6.1.2. The efficacy findings presented below are based on FDA adjudicated responses.

Table 13. STML-401-0114 – Primary Efficacy Measures

	Front Line			Relapsed/ Refractory
	Pivotal Cohort (Stage 3) N = 13	Stages 1 and 2 N = 16	All Stages N = 29	
• CR+CRc (95% CI)	7 (54%) (25, 81)	14 (88%) (62, 98)	21 (72%) (53, 87)	2 (13%) (2, 41)
• CR (95% CI)	3 (23%) (6, 54)	9 (56%) (31, 79)	12 (41%) (24, 61)	1
• CRc (95% CI)	4 (31%) (10, 61)	5 (31%) (12, 59)	9 (31%) (16, 51)	1

Source: FDA Analysis

Reviewer comment: The CR/CRc rate in the pivotal cohort (Stage 3) appears to be lower than

in Stages 1/2. However, the patient numbers are small, and the CR/CRc rate confidence intervals overlap. No significant difference was noted in patient characteristics between Stages 1/2 and Stage 3 to explain the difference in CR/CRc rate except for a greater percentage of subjects with high baseline blasts (> 40%) in the Stage 3 population (See Table 10).

7.1.2. Secondary and Other Endpoints

Table 14. STML-401-0114 – Secondary Efficacy Measures

	Front Line			Relapsed/ Refractory
	Pivotal Cohort (Stage 3) N = 13	Stage 1 and 2 N = 16	All Stages N = 29	
Duration of CR+CRc (months) Median (95% CI)	NE (7.3, NE)	NE (1.5, NE)	NE (5.9, NE)	3.7 and 13.9
Overall survival (months) Median (95% CI)	NE (5.2, NE)	NE (11.9, NE)	18.0 (9.7, NE)	7.1 (4.1, 11.9)
Time to CR (months) Median (95% CI)	1.9 (0.5, 2.7)	1.3 (0.7, 1.6)	1.4 (0.8, 1.6)	2.1 (1.5, 2.7)
Duration of follow-up (months) Median (95% CI)	11.5 (8.8, 11.9)	23.3 (13.7, 30.5)	17.6 (11.9, 26.9)	NE (6.6, NE)
SCT in CR/CRc	6/7	6/14	12/21	1/2
Time to SCT in CR/CRc (months) Range	4.2 (2.5, 6.7)	5.1 (3.7, 6.5)	4.6 (2.5, 6.7)	4.8

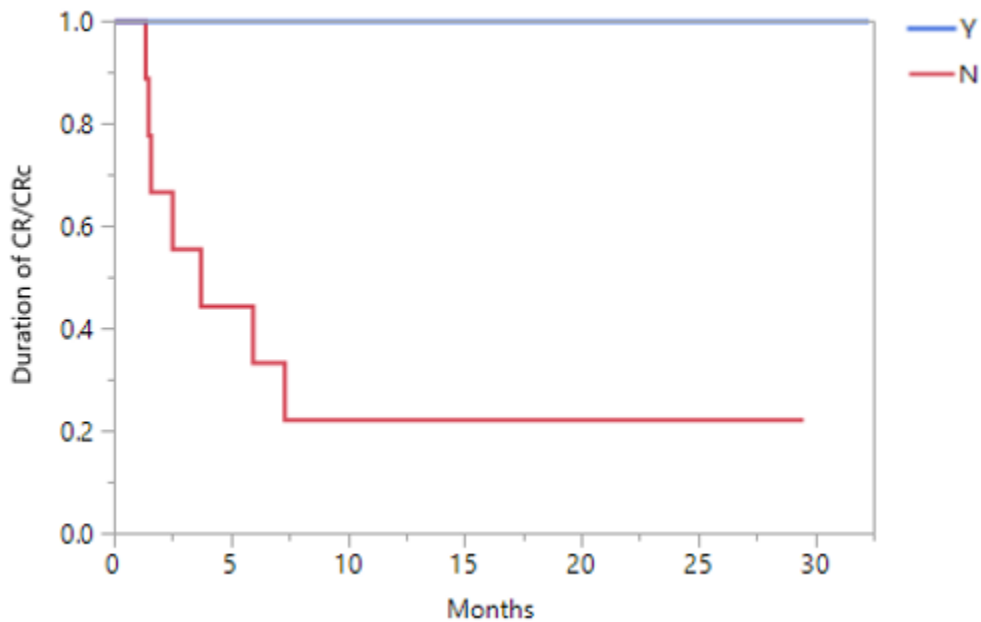
Source: FDA Analysis

Reviewer comment: In the pivotal cohort, the duration of CR/CRc was not reached with a median duration of follow-up of 11.5 months. Supportive data from Stages 1 and 2 who received front line treatment with tagraxofusp-erzs show that, with a longer duration of follow-up (median 23.3 months), the duration of CR/CRc was not reached.

7.1.3. Subpopulations

In general, there were too few subjects to perform meaningful subpopulation analyses on efficacy. However, one question of interest was whether the responses seen with tagraxofusp-erzs treatment were durable in the absence of subsequent transplantation.

Figure 3. STML-401-0114 – Duration of CR/CRc by Transplantation (Y/N) in Subjects Not Previously Treated for BPDCN



Transplantation in CR/CRc	N	Median duration of CR/CRc (months)	95% CI
Y	12	NR	(NE, NE)
N	9	3.7	(1.3, NE)

Source: FDA Analysis

Reviewer Comments: Responses do not appear to be durable in the absence of subsequent transplantation. This is consistent with historical reports in BPDCN. In the relapsed/refractory setting, of the 2 responders, the subject who went on to transplantation had a duration of response of 13.9 months.

7.1.4. Dose and Dose-Response

Little data are available on responses for subjects with BPDCN treated with other doses of tagraxofusp-erzs. No conclusions can be drawn regarding the dose of tagraxofusp-erzs and efficacy outcomes.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See discussions of Time to CR/CRc, Duration of CR/CRc in Secondary Endpoints

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

It is possible that, in the postmarket setting, tagraxofusp-erzs could be used off-label to treat CD123-positive AML. No statistically robust data are available on the efficacy of tagraxofusp-erzs use in this population. In STML-401-0114, among the 37 subjects with R/R AML treated with tagraxofusp-erzs at 12 µg/kg/day, the CR rate was 3% (1/37) (95% CI: 0.1, 14.2). Although these limited results show no efficacy in this disease, from a safety standpoint, there were no unique safety signals in AML (see Section 8). Therefore, there are insufficient data to support a limitation of use.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of tagraxofusp-erzs in BPDCN has been established based on the results of a single-arm, Phase 2 study in patients with BPDCN. Patients who received front line treatment with tagraxofusp-erzs 12 µg/kg/day on Days 1-5 of a 21-day cycle had a CR/CRc rate of 54% (95% CI: 25, 81) with a median duration of CR/CRc not reached (95% CI: 7.3, NE) (median follow-up 11.5 months [95% CI: 8.8, 11.9]). Two additional responses were seen in the relapsed/refractory population, with one response lasting 3.7 months and one lasting 13.9 months. Because tagraxofusp-erzs is a targeted therapy and pediatric BPDCN also expresses CD123, this efficacy outcome can be extrapolated to the pediatric population.

Data from the subjects in Stages 1 and 2 treated with tagraxofusp-erzs as front line therapy for BPDCN support the efficacy seen in the pivotal cohort. In this supportive cohort, the CR/CRc rate was 88% (95% CI: 62, 98) and the median duration of response was also not reached with a median follow-up of 23.3 months (95% CI: 13.7, 30.5).

8. Review of Safety

8.1. Safety Review Approach

The clinical review of safety for this BLA was based on all available safety data from studies STML-401-0114 and STML-401-0314 which enrolled subjects with myeloid malignancies (BPDCN, AML, and MPN) with active disease treated with tagraxofusp-erzs monotherapy. The 60-day safety update data set (Module 5.3.5.3) was used for the safety analyses. This population is referred to as the “Full Safety Population” in this review. Of note, the 60-day safety update included safety data from an additional 14 subjects with BPDCN treated in Stage 4 of STML-401-0114 after the data cut-off for the primary efficacy analysis; therefore, the total number of subjects with BPDCN is higher in the safety review than in Sections 6 and 7.

Beginning with Section 8.4.4, parts of the safety review focus specifically on subjects from STML-401-0114 with active disease (BPDCN or AML) treated with tagraxofusp-erzs at the 12 mcg/kg/day dose on days 1-5 of a 21-day cycle. Safety analyses in these subjects are particularly relevant to labeled dose and schedule; this population is referred to as the “Focused Safety Population” in this review.

Three children were treated outside of clinical trials at the 12 mcg/kg/day dose on days 1-5 of a 21-day cycle, and the safety experience for these subjects is described in Section 8.8.3.

Table 15. Studies Contributing to Overall Safety

Protocol	Population	Dose	Regimen	Maximum Cycles
STML-401-0114	Adult, any BPDCN and R/R AML N = 110	7-16 µg/kg/day	Days 1-5 of 21-day cycle	Indefinite
STML-401-0314	Adult, advanced, high risk MPN N = 29	7-16 µg/kg/day	Cycles 1-4: Days 1-3 of 21-day cycle Cycles 4-7: Days 1-3 of 28-day cycle Cycle 8+: Days 1-3 of 42-day cycle	Indefinite

Additional safety information

The applicant also submitted data from STML-401-0214, a single-arm trial of 16 subjects with AML in CR who were treated with tagraxofusp-erzs monotherapy maintenance. Because these subjects do not have active disease and are expected to be relatively fit at baseline, inclusion of these subjects in pooled analyses might skew the results of the safety analyses. Therefore,

these subjects are discussed separately in Section 8.9.5 except for deaths which are discussed in Section 8.4.1.

The applicant also submitted data from STML-401-0414, a single-arm trial of 7 subjects with multiple myeloma who were treated with tagraxofusp-erzs in combination with pomalidomide and dexamethasone. These subjects are not included in the pooled review of safety and are discussed briefly in Section 8.9.5.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 139 subjects with active disease received at least one dose of tagraxofusp-erzs monotherapy and are included in the full safety population. The median treatment exposure was 46 days, with a median of 3 cycles of tagraxofusp-erzs started (Table 16). Four subjects in the full safety population have received tagraxofusp-erzs for over one year.

Table 16. Full Safety Population – Tagraxofusp-erzs Exposure by Disease

	BPDCN N = 61	AML N = 49	MPN N = 29	Pooled N = 139
Median treatment exposure (days)	72	6	72	46
Range	2-927	2-410	3-406	2-947
25-75 percentile	29-111	5-32	25-123	6-95
Median number of cycles started	4	1	4	3
Range	1-43	1-18	1-14	1-43
25-75 percentile	3-6	1-2	2-6	1-5
Median total doses received	18	5	12	10
Range	2-212	2-87	3-42	2-212
25-75 percentile	10-25	4-10	6-17	5-20

Source: FDA analysis

Table 17. Full Safety Population – Tagraxofusp-erzs Exposure by Dose Level

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	2 (67%)	1 (33%)	-	-

		(0.2-3.6)				
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%)

*Focused Safety Population
Source: FDA Analysis

8.2.2. Relevant characteristics of the safety population:

The applicant provided a dataset containing adverse event occurrences in the 2 trials listed in Table 15. The full safety population includes 61 subjects with BPDCN and 78 subjects with other hematologic malignancies (AML and MPN) who were treated with tagraxofusp-erzs monotherapy at various doses and on various dose schedules. Key characteristics of these populations are shown in Table 18.

Table 18. Demographics of the Full Safety Population

	BPDCN N = 61 n	AML/MPN N = 78 n	Pooled N = 139 n
Gender			
Female	8 (13%)	34 (44%)	42 (30%)
Male	53 (87%)	44 (56%)	97 (70%)
Age (Years)			
Median (Range)	69 (22-84)	66.5 (21-87)	67 (21-87)
18 - <65 years	23 (38%)	36 (46%)	59 (42%)
65 - <75 years	22 (36%)	27 (35%)	49 (35%)
≥ 75 years	16 (26%)	15 (19%)	31 (22%)
ECOG			
0	27 (44%)	14 (18%)	41 (29%)
1-2	33 (54%)	53 (68%)	86 (62%)
Unknown	1 (2%)	11 (14%)	12 (9%)

Race			
White	55 (90%)	63 (81%)	118 (85%)
Black	2 (3%)	4 (5%)	6 (4%)
Asian	2 (3%)	7 (9%)	9 (7%)
Other	2 (3%)	4 (5%)	6 (4%)
Diagnosis			
BPDCN	61 (100%)	-	61 (44%)
AML	-	49 (63%)	49 (35%)
Myeloproliferative neoplasm	-	29 (37%)	29 (21%)
Treatment Status			
No prior therapy for diagnosis	45 (74%)	1 (1%)	46 (33%)
Relapsed/refractory	16 (26%)	48 (62%)	64 (46%)
Not specified (MPN)	-	29 (37%)	29 (21%)
Tagraxofusp-erzs dose			
<u>5-day schedule:</u>			
7 µg/kg/day	3 (5%)	3 (4%)	6 (4%)
9 µg/kg/day	-	3 (4%)	3 (2%)
12 µg/kg/day	58 (95%)	36 (46%)	94 (%)
16 µg/kg/day	-	7 (9%)	7 (5%)
<u>3-day schedule:</u>			
7 µg/kg/day	-	3 (4%)	3 (2%)
9 µg/kg/day	-	3 (4%)	3 (2%)
12 µg/kg/day	-	23 (29%)	23 (16%)

*Focused safety population

Source: FDA Analysis (SAFFL = Y)

Key characteristics of subjects with active myeloid malignancies treated with the proposed labeled dose (12 µg/kg/day) and schedule (5 days) are shown below in Table 19. This is the population used to support labeling.

Table 19. Demographics of the Focused Safety Population

	BPDCN N = 58 n	AML N = 36 n	Pooled N = 94 n
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%)

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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			
No prior therapy for diagnosis	42 (72%)	1 (3%)	43 (46%)
Relapsed/refractory	16 (28%)	32 (89%)	48 (51%)

Source: FDA Analysis (SAFFL = Y, TRT01A = 12 mcg/kg/day)

8.2.3. Adequacy of the safety database:

Reviewer Comment: Overall, the demographics of the safety population are consistent with those of the intended population. There were no pediatric subjects treated with tagraxofusp-erzs in the applicant's trials for any diagnosis. Although BPDCN is a rare disease, there are reports in the literature of BPDCN occurring in subjects of all ages from as young as 8 months. Data from 3 pediatric subjects treated with tagraxofusp-erzs (b) (4) are discussed in Section 8.9.3 of this review.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No major issues involving data integrity or submission quality were identified.

8.3.2. Categorization of Adverse Events

Adverse events were reported down to the verbatim term and were coded using MedDRA version 19.0. CTCAE version 4.03 was used for toxicity grading. Treatment-emergent adverse events (TEAE) excluded events starting and ending before the start of study drug. FDA administered custom queries for selected adverse events of special interest (see Appendix 13.3 for FDA's grouped terms).

8.3.3. Routine Clinical Tests

Routine clinical tests included vital signs, CBC, chemistry, coagulation parameters, and urinalysis. The frequency of the monitoring was considered adequate.

8.4. Major Safety Results

8.4.1. Deaths

For the assessment of deaths, the applicant looked at any subjects who experienced a Grade 5 treatment-emergent adverse event. The applicant identified 17 subjects with fatal adverse events. The most common fatal adverse events were capillary leak syndrome, sepsis, and intracranial hemorrhage (AML subjects only).

FDA identified 85 deaths among 155 subjects exposed to tagraxofusp-erzs monotherapy. Most deaths occurred more than 30 days after the last dose of tagraxofusp-erzs (81%).

Table 20. Deaths

Category	BPDCN N=61	Other Active Disease (AML, MPN) N=78	AML in CR N = 16
Total deaths	30 (49%)	56 (72%)	3 (19%)
30-day mortality ¹	4 (7%)	9 (12%)	0
60-day mortality ¹	4 (7%)	16 (21%)	0
On-treatment deaths ²	4 (7%)	12 (15%)	0
Fatal ARs	3 (5%)	4 (5%)	-
Primary disease	1 (2%)	5 (6%)	-
Intercurrent condition	0	3 (4%)	-

Source: FDA analysis

¹Within 30 or 60 days following the first dose of therapy

²On or within 30 days after the last dose of therapy

Narratives were provided for all subjects who died within 30 days after the last dose of tagraxofusp-erzs. FDA reviewed all narratives and any available laboratory values from the ADLB data file to confirm the cause of death. The narratives in the original submission were generally of acceptable quality, but occasionally differed from the ADSL data file variable DTHRS.

FDA considered the cause of death to be the primary malignancy when supported by worsening of disease by blast count, imaging report or description of other objective evidence.

FDA reviewed narratives and/or other available data for all fatal AEs and all on-treatment deaths. Of the 16 on-treatment deaths, the applicant-reported causes of death were primary disease (n=6), fatal ARs (n=7) including capillary leak syndrome, MI, and sepsis/infection, or other intercurrent ARs (n=3). FDA agreed with the Sponsor's assessment of causality for most

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deaths except for 3 subjects: STML-401-0114- (b) (6), STML-401-0114- (b) (6) and STML-401-0314- (b) (6).

Table 21. Deaths Suspected by FDA As Related to Tagraxofusp-erzs

Disease	Subject	Death Day	Days Since Last Dose	Dose µg/kg/day	FDA Root COD	Investigator Root COD
BPDCN	STML-401-0114- (b) (6)	19	14	7	AR – CLS	AR – CLS (related)
BPDCN	STML-401-0114- (b) (6)	9	3	12	AR – CLS	AR – MI (unrelated)
BPDCN	STML-401-0114- (b) (6)	7	5	12	AR – CLS	AR – CLS (related)
AML	STML-401-0114- (b) (6)	5	2	16	AR – CLS	AR – CLS (related)
AML	STML-401-0114- (b) (6)	4	1	16	AR – CLS	Study disease (unrelated)
MPN	STML-401-0314- (b) (6)	15	12	12 (3-day schedule)	AR – CVA	AR – CVA (unrelated)

Source: FDA analysis

Abbreviations: AR, adverse reaction; CLS, capillary leak syndrome; COD, cause of death; CRS, cytokine release syndrome; CVA – cerebrovascular accident; MI, myocardial infarction

There were 4 deaths considered by FDA to be a direct toxicity of tagraxofusp-erzs. The narrative for the subject in whom the applicant considered COD to be unrelated is below.

STML-401-0114- (b) (6) – Narrative: 79yo M with BPDCN received front line tagraxofusp-erzs 12 µg/kg/day. Total doses: 5.

On Day 2, he developed signs of CLS including 2kg weight gain, dyspnea with SpO2 89%, and fever (temperature not reported). The second infusion was held. EKG revealed atrial fibrillation. Blood cultures, X-ray, and urinalysis were negative. The subject received a diuretic, methylprednisolone, supplemental oxygen, and cefepime. Symptoms resolved, and the subject received infusions 2 and 3 on Days 4 and 5 respectively. Although his liver enzymes were elevated (actual values not reported), he received infusion 4 on Day 6 after which he developed “significantly” elevated LFTs with AST > 5x ULN. Tagraxofusp-erzs was discontinued. On Day 8 (2 days after the last dose) steroid treatment was discontinued. AST and ALT were 594 U/L and 161 U/L, respectively. That evening, the subject again experienced dyspnea and CXR revealed pulmonary edema. He received diuretic, supplemental oxygen, and albuterol and was considered stabilized. The following morning, he was found to be non-responsive and

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subsequently died. Based on autopsy, COD was considered to be Grade 5 MI reported as unrelated to tagraxofusp-erzs; the subject had ongoing Grade 4 pulmonary edema at time of death (considered related to tagraxofusp-erzs).

Labs (ADLB): Baseline albumin – 41-44 g/L. Days 5-7: fluctuating between 30-33 g/L

Reviewer comment: The applicant concluded that myocardial infarction was the cause of death and was unrelated to tagraxofusp-erzs. FDA disagrees with this assessment. This subject had dyspnea and hypoxia requiring supplemental oxygen, diuresis, and steroids, and he had a 25% drop in albumin from baseline. Despite a brief symptomatic reprieve with supportive care, shortly after stopping steroids the dyspnea recurred with evidence of Grade 4 pulmonary edema and the subject died within 1 day. This subject was still clearly experiencing signs/symptoms consistent with capillary leak syndrome.

There were 2 deaths considered by FDA to be at least possibly related to tagraxofusp-erzs in whom the applicant considered COD to be unrelated. The narratives are provided below.

STML-401-0114- (b) (6) – Narrative: 58yo F with R/R AML received tagraxofusp-erzs 16 µg/kg/day. Total doses: 2

On Day 2, study drug was held due to increase in body weight ≥ 1.5 kg above baseline, Grade 1 hypoalbuminemia, Cr 60 µmol/L. On Day 3, Grade 2 DIC (low platelets) was reported in the narrative, but subject did receive dose 2. On Day 4, Grade 2 blood creatinine was diagnosed (Cr 106 µmol/L) and SAE of tumor lysis syndrome was reported. CXR revealed atelectasis. On Day 5, Cr 229 µmol/L, fibrinogen and INR were within normal limits, PT and PTT elevated, LDH 4110 U/L, and uric acid 4.8 mg/dL (WNL). CXR showed bilateral airspace disease. The subject developed increase oxygen requirement and altered mental status as well as Grade 2 acute kidney injury with rapidly increasing creatinine and decreased urine output (values not provided). Physical exam revealed fluid overload and treatment included furosemide, supplemental O2, sevelamer, and allopurinol. On Day 6, the subject was transferred to the ICU for treatment of tumor lysis syndrome and continuous veno-venous hemofiltration. On Day 7, the subject showed some initial improvement, but her respiratory status declined throughout the day. CXR showed development of lateral diffuse airspace disease, likely representing edema. Dialysis was stopped on Day 7 and subject died due to study disease.

Labs (ADLB):

	Day 1 Dose 1	Day 2	Day 3 Dose 2	Day 4	Day 5 Allopurinol started	Day 6 Dialysis started	Day 8
Creatinine (µmol/L)	60	81	68	106	229*	223*	91
Urate (µmol/L)	285	107	231	321	422*	327	154

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Potassium (mmol/L)	4	3.6	4.5	4.3	4.2	4.4	3.6
Phosphate (mmol/L)	2.3	0.9	1.4	1.7*	1.6*	1.5	0.7
Calcium (mmol/L)	2.2	2.1^	2.3	2.3	2.3	2.3	
WBC (10 ⁹ /L)	9.4	9.6	19.9*	22.9*	28.8*	23*	9.1*
Blasts (%)	7.4*			22*	46*		
Platelets (10 ⁹ /L)	67^		62^	16^	80^		32^

* Greater than upper limit of normal

^ Less than lower limit of normal

Reviewer comment: Although this subject has active disease and a PT of tumor lysis syndrome, her lab values are not convincing for TLS. Weight gain and hypoalbuminemia were reported after the first dose of tagraxofusp-erzs and prior to the increased WBC count, and an inflammatory response to tagraxofusp-erzs may have contributed to the subsequent leukocytosis. CLS secondary to tagraxofusp-erzs cannot be ruled out as a possible cause of renal failure and death for this subject.

STML-401-0314- (b) (6) - Narrative: 63yo M with advanced symptomatic systemic macrocytosis received tagraxofusp-erzs 12 µg/kg/day as second line therapy. Total doses: 3

On Day 6 (3 days after the last dose) the subject developed Grade 3 tumor lysis syndrome as reported in the narrative but has a preferred term of Grade 2 CLS recorded in ADAE. On Day 7, he was hospitalized for evaluation of severe exertional dyspnea. There was no edema and no focal neurological deficits or cranial nerve abnormalities on exam. WBC 17 Gi/L, ANC 18 Gi/L, 20% monocytes, platelets 131 Gi/L, elevated transaminases (values not provided). He was noted to have slight weight gain and decreased serum albumin (value not provided). Echo showed LVEF 63% with no right wall motion abnormalities, localized pericardial effusion around the right ventricle and right atrium with circumferential pericardial effusion. A baseline echocardiogram done 1 year prior showed pericardial effusion, and the current complaint of dyspnea was attributed to recurrent pericardial effusion (previous episode due to underlying mastocytosis). Repeat echo the following morning was stable. The same day (Day 9), he developed right-sided hemiparesis the evolved into hemiplegia with dysarthria. CT scan and angiogram showed complete occlusion of the left internal carotid artery with collateralization. Attempted mechanical thrombolysis was unsuccessful. On Day 10, MRI with venogram demonstrated probably partial thrombosis of left cavernous sinus with extensive left cerebral hemispheric infarction, and the subject's neurological status deteriorated over the next 24 hours. Thrombophilia was noted with unclear etiology. On Day 14, CT showed left MCA infarct with significant midline shift due to cerebral edema. The subject was placed on palliative care and died on Day 15, 12 days after the last dose of study drug. The investigator considered CLS, pericardial effusion, and cerebrovascular accident to be related to study drug. The Applicant considered CVA unlikely related to study drug.

Autopsy concluded the immediate cause of death was thrombosis of the left ICA with infarction of the left cerebral hemisphere and cerebral edema with mass effect compression and uncal herniation. Contributing condition: CMML and systemic mastocytosis with marked splenomegaly. Additional findings: systemic changes of hypertension.

Reviewer comment: Although the subject had evidence of long-standing occlusion of the left ICA (collateralization noted on CT), given the rapid progression of events after receiving study drug and preceded by an inflammatory state with capillary leak syndrome, the contribution of study drug to CVA cannot be ruled out. This event is considered at least possibly related to tagraxofusp-erzs.

8.4.2. Serious Adverse Events

Serious adverse events occurring within 30 days of the last dose of tagraxofusp-erzs are shown in the table below by SOC in decreasing order of incidence in the BPDCN population.

Table 22. Full Safety Population – Serious Adverse Events within 30 Days of Follow-Up

System Organ Class	BPDCN N = 61		AML/MPN N = 78		Pooled N = 139	
	n	%	n	%	n	%
Any Class	32	53%	50	64%	82	59%
Vascular disorders	8	13%	12	15%	20	14%
General disorders and administration site conditions	6	10%	10	13%	16	12%
Infections and infestations	3	5%	17	22%	20	14%
Respiratory, thoracic and mediastinal disorders	3	5%	8	10%	11	8%
Cardiac disorders	3	5%	5	6%	8	6%
Metabolism and nutrition disorders	3	5%	5	6%	8	6%
Investigations	3	5%	3	4%	6	4%
Musculoskeletal and connective tissue disorders	3	5%	0	0%	3	2%
Blood and lymphatic system disorders	2	3%	10	13%	12	9%
Nervous system disorders	2	3%	7	9%	9	6%
Gastrointestinal disorders	1	2%	5	6%	6	4%
Injury, poisoning and procedural complications	1	2%	3	4%	4	3%
Skin and subcutaneous tissue disorders	1	2%	1	1%	2	1%
Eye disorders	1	2%	0	0%	1	1%

Immune system disorders	1	2%	0	0%	1	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2%	0	0%	1	1%
Renal and urinary disorders	0	0%	3	4%	3	2%
Ear and labyrinth disorders	0	0%	1	1%	1	1%
Hepatobiliary disorders	0	0%	1	1%	1	1%

Source: FDA Analysis

Investigations and metabolism/nutrition disorders were the most common TEAE leading to treatment interruption or withdrawal (Section 8.4.3). In the BPDCN subgroup, events resulting in treatment interruption or withdrawal were from the SOC Investigations for 31 (51%) subjects and from the SOC Metabolism and nutrition disorders for 12 (20%) subjects. Preferred terms under SOC Investigations were those relating to elevated LFTs and weight increases. Preferred terms under SOC Metabolism and nutrition disorders were predominantly hypoalbuminemia and tumor lysis syndrome.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 78 (56%) of treated subjects had a dose delay or permanent discontinuation, including 36 (59%) of the subjects in the BPDCN subgroup. The percentages of subjects with either an interruption or a permanent discontinuation due to an adverse event are shown in Table 23.

Table 23. Full Safety Population – Treatment Delay or Withdrawals

	BPDCN N = 61		AML/MPN N = 78		Pooled N = 139	
	n	%	n	%	n	%
Treatment Delay	33	54%	30	38%	63	45%
Treatment Withdrawal	3	5%	12	15%	15	11%
Any	36	59%	42	54%	78	56%

Source: FDA Analysis

The most common TEAE resulting in treatment delay or permanent discontinuation are shown in Table 24 in decreasing order in the BPDCN subgroup. The table includes only those events that occurred in $\geq 2\%$ of subjects in either subgroup.

Table 24. Full Safety Population – TEAEs Resulting in Treatment Delay or Withdrawal

Preferred Term*	BPDCN N = 61		AML/MPN N = 78		Pooled N = 139	
	n	%	n	%	n	%

TEAE with Delay						
CLS signs/symptoms	27	44%	23	29%	50	36%
• Weight increased	15	25%	9	12%	24	17%
• Hypoalbuminemia	8	13%	9	12%	17	12%
• Capillary leak syndrome	4	7%	5	13%	9	6%
• Hypotension	2	3%	1	7%	3	2%
• Infusion related reaction	2	3%	-	-	2	1%
Elevated LFTs	16	26%	6	8%	22	16%
Pyrexia	7	11%	7	9%	14	10%
CLS/infusion reaction	5	8%	5	6%	10	7%
Arrhythmia	2	3%	-	-	2	1%
TEAE with Withdrawal [^]						
Elevated LFTs	2	3%	-	-	2	1%
CLS signs/symptoms	1	2%	3	6%	4	3%
• Hypoalbuminemia	1	2%	2	3%	3	2%
• CLS/IRR	-	-	2	3%	2	1%
Cerebrovascular accident	-	-	2	3%	2	1%
Acute kidney injury	-	-	2	3%	2	1%

*Includes Grouped Terms

[^] Module 2.7 Clinical Summary states that Grade 5 TEAEs were not necessarily captured as TEAEs leading to discontinuation.

Source: FDA Analysis

The table above is based on AEs in the ADAE data file coded with AEACN = “Drug interrupted” or “Drug withdrawn”. However, as noted in the footnote, the Clinical Summary (page 62) states that Grade 5 TEAEs were not necessarily captured as having led to tagraxofusp-erzs discontinuation. Based on narratives for the 17 subjects with Grade 5 TEAEs, an additional 3 subjects (STML-401-0114- (b) (6)) were considered to have discontinued due to CLS signs/symptoms, making it the leading cause for treatment withdrawal across the safety population (BPDCN – 3%, Other – 6%, Pooled – 5%). Other reasons for discontinuation according to subjects’ narratives included physician decision and progressive disease.

An additional 6 subjects (4 BPDCN, 1 AML, 1 MPN) had their dose of tagraxofusp-erzs reduced from 12 to 9 µg/kg/day in subsequent cycles. Reasons given included multiple sclerosis relapse, transient ischemic attack during previous cycle, AST increased during previous cycle, and history of infusion related reaction.

Reviewer Comment: The high rate of capillary leak signs/symptoms requiring dose interruption or withdrawal is a concern, and the range of manifestations of capillary leak syndrome may complicate management in the postmarketing period. Labeling should include a warning that addresses the incidence of capillary leak syndrome (see also 8.4.4) and that

describes the possible manifestations and appropriate management. Hepatotoxicity was also a significant cause of dose delay or withdrawal and merits close monitoring (see 8.5.2. for further discussion).

8.4.4. Significant Adverse Events/Adverse Events of Special Interest

Capillary Leak Syndrome

Capillary leak syndrome is a toxicity observed with many drugs including other immunotoxins such as denileukin difitox (diphtheria toxin) and moxetumomab (*Pseudomonas* endotoxin), as well as drugs like gemcitabine and clofarabine. Furthermore, the risk of CLS may be higher with tagraxofusp-erzs because it targets the IL-3 receptor which is also expressed on vascular endothelial cells. CLS is characterized by an acute phase during which leakage of fluid and proteins from the intravascular space to the interstitium results in hypotension, edema, and hypoalbuminemia. During the resolution phase, mobilization of fluid back into circulation can result in fatal pulmonary edema, especially after intensive fluid resuscitation during the acute phase.

In the clinical setting, cytokine release syndrome (CRS) and infusion related reactions (IRR) are difficult to distinguish from CLS because the clinical manifestations and timing overlap; furthermore, the proinflammatory states seen in CRS and IRR can evolve into subsequent CLS.

The preferred term “capillary leak syndrome” was reported in all subject populations and at all dose levels of tagraxofusp-erzs studied.

Table 25. Full Safety Population – Signs/Symptoms of CLS by Individual Preferred Terms within 30 days of Follow-Up

Preferred Term	BPDCN N = 61		AML N = 49		MPN N = 29		Pooled N = 139	
	n	%	n	%	n	%	n	%
Any Grade								
Hypoalbuminaemia	33	54%	30	61%	13	45%	63	45%
Oedema peripheral	30	49%	19	39%	15	52%	49	35%
Weight increased	22	36%	11	22%	6	21%	33	24%
Hypotension	17	28%	16	33%	7	24%	33	24%
Capillary leak syndrome	12	20%	10	20%	5	17%	22	16%
Dyspnoea	8	13%	18	37%	14	48%	26	19%
Fluid overload	5	8%	1	2%	2	7%	6	4%
Cytokine release syndrome	3	5%	-	-	-	-	3	2%

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Infusion related reaction	3	5%	2	4%	-	-	5	4%
Peripheral swelling	3	5%	2	4%	1	3%	5	4%
Fluid retention	2	3%	2	4%	-	-	4	3%
Pulmonary oedema	2	3%	3	6%	1	3%	5	4%
Swelling face	2	3%	-	-	-	-	2	1%
Hypervolaemia	1	2%	-	-	-	-	1	1%
Localised oedema	1	2%	-	-	-	-	1	1%
Tongue oedema	1	2%	-	-	-	-	1	1%
Ascites	-	-	1	2%	-	-	1	1%
Eyelid oedema	-	-	1	2%	-	-	1	1%
Face oedema	-	-	1	2%	-	-	1	1%
Generalised oedema	-	-	1	2%	1	3%	1	1%
Laryngeal oedema	-	-	1	2%	-	-	1	1%
Periorbital oedema	-	-	1	2%	-	-	1	1%
Swelling	-	-	1	2%	-	-	1	1%
Grade ≥ 3								
Hypotension	5	8%	4	8%	2	7%	9	6%
Capillary leak syndrome	4	7%	3	6%	1	3%	7	5%
Pulmonary oedema	2	3%	-	-	1	3%	2	1%
Infusion related reaction	1	2%	1	2%	-	-	2	1%
Dyspnoea	1	2%	1	2%	2	7%	2	1%
Cytokine release syndrome	1	2%	-	-	-	-	1	1%
Hypoalbuminemia	-	-	1	2%	-	-	1	1%
Fluid overload	-	-	1	2%	-	-	1	1%
Generalised oedema	-	-	1	2%	-	-	1	1%
Oedema peripheral	-	-	1	2%	-	-	1	1%

Source: FDA Analysis

Although high grade CLS events were more likely to have been correctly coded with the preferred term of “capillary leak syndrome,” it was noted during the safety review that the constituent signs and symptoms typical of CLS (i.e. hypotension, hypoalbuminemia, and edema) were reported individually more frequently than the preferred term was reported (see Table 25 above). FDA was concerned that the incidence of low-grade CLS might be underreported when based on MedDRA PT alone, so the full safety population was screened for possible cases of CLS based on the following algorithm.

Screen-positive subjects included those

- With Preferred Term “Capillary leak syndrome” as an adverse event, OR
- Those meeting 2 or more of the criteria in the table below with at least 2 criteria having a start date within 7 days of each other.

Table 26. FDA Capillary Leak Syndrome Screening Criteria

Criteria	Variable	Value
≥ 1 of these (Hypoalbuminemia)	PT	Hypoalbuminaemia
	Lab result	Albumin (<i>any value</i> ≤ 3 g/dL)
≥ 1 of these (Edema)	HLT	Oedema
	PT	Ascites
	PT	Eyelid oedema
	PT	Face oedema
	PT	Fluid overload
	PT	Fluid retention
	PT	Generalized oedema
	PT	Hypervolaemia
	PT	Laryngeal oedema
	PT	Oedema
	PT	Oedema peripheral
	PT	Periorbital oedema
	PT	Peripheral swelling
	PT	Swelling
	PT	Swelling face
	PT	Weight increased
	VS result	Weight (<i>any value</i> > 5 kg from baseline)
≥ 1 of these (Hypotension)	PT	Hypotension
	PT	Hypovolemia
	VS result	Systolic Blood Pressure (<i>any value</i> < 90 mmHg)
	Concomitant medication	Dopamine
	Concomitant medication	Ephedrine
	Concomitant medication	Epinephrine
	Concomitant medication	Norepinephrine
	Concomitant medication	Norepinephrine bitartrate
	Concomitant medication	Phenylephrine
	Concomitant medication	Vasopressin
≥ 1 of these (CRS/IRR)	PT	Cytokine release syndrome
	PT	Infusion related reaction

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("Catch-all")	PT	Cardiac arrest
	PT	Cardiopulmonary failure
	PT	Multi-organ failure
	PT	Multiple organ dysfunction syndrome

Subjects identified by the screening algorithm were then independently adjudicated based on narratives (if present in the submission) and all data available in the dataset including reported AEs, laboratory values, vital signs, and concomitant medications.

Twenty-seven subjects (19%) in the full safety population and 22 subjects (19%) in the focused safety population had a reported PT of "capillary leak syndrome" (any grade). The screening algorithm identified a total of 81 subjects (58%) in the full safety population and 66 subjects (56%) in the focused safety population with possible CLS at any time on study.

In the full safety population, FDA excluded:

1. Subjects with a narrative or other data consistent with sepsis/infection with an identified source as a potential secondary cause of symptoms (n=4)
2. Subjects in whom one criteria was rejected (i.e. pressors given as procedural standard of care for bone marrow biopsy (i.e. not to treat hypotension); report of SBP < 90 mmHg prior to start of treatment (Day -4) but normal SBP throughout treatment; weight gain > 5 kg above baseline where weight had been stably 4 kg above baseline for an extended period) and who did not otherwise meet 2 or more of the listed criteria (n=3)
3. One subject who came off study in Cycle 1 due to progressive disease and was reported to have Grade 2 hypoalbuminemia and generalized oedema >30 days after end of treatment
4. One subject in whom "multiple organ dysfunction syndrome" was reported was excluded based on a narrative describing hemorrhagic shock due to an abdominal wall hematoma in the setting of concomitant anticoagulant use (for a prior thrombotic event) and specifically noted to have "no evidence of CLS."
5. All AEs coded with the PT of "cytokine release syndrome" or "infusion related reaction" were assessed individually and excluded only if there were no potentially overlapping manifestations described (i.e. one subject with infusion-related reaction described only as back pain was excluded).

CLS could not be excluded in subjects with a preferred term of CRS or IRR described as having hypotension, edema, or hypoalbuminemia or in whom no narrative was provided.

Although many events lacked corresponding narratives describing symptomology, a rough attempt was made to estimate severity based on the CTCAE grades of the component criteria and the intensity of any reported interventions. Events were given composite CLS grades A-E.

Grades of Composite CLS

- A – All Components = Grade 1 AND no interventions or dose delays (or Grade 1 PT CLS)
- B – ≥ 1 Component = Grade 2 OR Grade 1-2 with albumin or IV fluid infusions or resulting in dose delay per protocol (or Grade 2 PT CLS)
- C – ≥ 1 Component = Grade 3 OR pressors or steroids (or Grade 3 PT CLS)
- D – ≥ 1 Component = Grade 4 OR intubation or dialysis required (or Grade 4 PT CLS)
- E – Fatal CLS (or Grade 5 PT CLS)

Based on our adjudication, there were 76 possible CLS events in 70 subjects from the Full Safety Population. An additional subject, STML-401-0114- (b) (6), was identified in whom CLS and CRS were reported in the narrative only without corresponding entries in the ADAE data file. This subject is included in FDA analyses below as having had CLS. Based on these analyses, 71/139 (51%) subjects in the Full Safety Population (Table 27) and 52/94 (55%) in the Focused Safety Population experienced an adverse reaction of CLS. There were no significant differences in the overall incidence of CLS based on dose or schedule of tagraxofusp-erzs (Table 28).

Table 27. Full Safety Population – Highest Grade CLS Event by Preferred Term Only vs Composite CLS

N = 139	Grade 1/A	Grade 2/B	Grade 3/C	Grade 4/D	Grade 5/E	All Grades	Grades 3-5/C-E
PT CLS only	-	19 (14%)	3 (2%)	2 (1%)	3 (2%)	27 (19%)	8 (6%)
Composite CLS	7 (5%)	51 (37%)	6 (4%)	2 (1%)	5 (4%)	71 (51%)	13 (9%)

Source: FDA Analysis

Table 28. Full Safety Population – CLS by Tagraxofusp-erzs Dose

Dose	N	All Grades		Grade ≥ 3/C	
		PT CLS only	Composite CLS	PT CLS only	Composite CLS
5-Day Schedule					
7 µg/kg/day	6	1 (17%)	4 (67%)	1 (17%)	1 (17%)
9 µg/kg/day	3	1 (33%)	2 (67%)	-	-
12 µg/kg/day^	94	17 (18%)	52 (55%)	4 (4%)	8 (9%)
16 µg/kg/day	7	3 (43%)	5 (71%)	2 (29%)	3 (43%)
3-Day Schedule					
7 µg/kg/day	3	-	-	-	-
9 µg/kg/day	3	1 (33%)	1 (33%)	-	-

12 µg/kg/day	23	4 (17%)	7 (30%)	1 (4%)	1 (4%)
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^Focused safety population

Source: FDA Analysis

As expected, a majority of cases were low grade events occurring in Cycles 1-2 (Tables 29 and 30). However, an additional 5 high grade events (Grade C and E) were identified including two additional fatal cases of CLS described in 8.4.1. Five subjects in the Full Safety Population were adjudicated as having had CLS in both Cycles 1 and 2. One subject had CLS in Cycles 1 and 5.

Table 29. Full Safety Population – CLS in Cycles 1 and 2

	BPDCN		AML/MPN		Pooled	
	All Grades	Grade ≥ 3/C	All Grades	Grade ≥ 3/C	All Grades	Grade ≥ 3/C
Cycle 1	N = 61		N = 78		N = 139	
• PT CLS only	12 (20%)	4 (7%)	14 (18%)	4 (5%)	26 (19%)	8 (6%)
• Events identified by screening algorithm	31	-	38	-	69	-
• Composite CLS	31 (51%)	6 (10%)	33 (42%)	6 (7%)	64 (46%)	12 (9%)
Cycle 2	N = 52		N = 49		N = 101	
• PT CLS only	1 (2%)	0	1 (2%)	0	4 (4%)	0
• Events identified by screening algorithm	6	-	8	-	14	-
• Composite CLS	5 (10%)	1 (2%)	5 (10%)	0	10 (10%)	1 (1%)

Source: FDA Analysis

Table 30. Focused Safety Population – CLS in Cycles 1 and 2

	BPDCN		AML		Pooled	
	All Grades	Grade ≥ 3/C	All Grades	Grade ≥ 3/C	All Grades	Grade ≥ 3/C
Cycle 1	N = 58		N = 36		N = 94	
• PT CLS only	11 (19%)	3 (5%)	5 (14%)	1 (3%)	16 (17%)	4 (4%)
• Events identified by screening algorithm	29	-	21	-	50	-
• Composite CLS	29 (50%)	5 (9%)	18 (50%)	2 (6%)	47 (50%)	7 (7%)
Cycle 2	N = 52		N = 49		N = 101	
• PT CLS only	3 (%)	2 (4%)	2 (4%)	0	5 (5%)	2 (2%)
• Events identified by screening algorithm	6	-	4	-	10	-
• Composite CLS	5 (10%)	1 (2%)	2 (4%)	0	7 (7%)	1 (1%)

Source: FDA Analysis

The algorithm also identified 3 subjects in the Focused Safety Population with possible CLS in Cycles 3 and 11. Of these, the 2 subjects in Cycle 3 were thought to have Grade B CLS.

Time to CLS

The Applicant notes that the median time to CLS was 6.5 days (range 4-51) in subjects with BPDCN and 5 days (range 4-29) in subjects with AML (based on timing of preferred term of CLS). For all subjects with composite CLS, the median time to earliest symptom was 4 days (range 1-96). In the Focused Safety Population, the median time to earliest symptom was also 4 days (BPDCN range – 1-46; AML range 1-31).

Treatment of CLS

The protocol provided instructions for holding tagraxofusp-erzs for hypotension, weight increases, hypoalbuminemia, and CLS and included basic supportive care instructions for the administration of albumin, diuretics, and steroids. However, 6 subjects required intensification of care for management of their CLS (Table 31). Based on a review of the narratives for all Grade ≥ 3 /C FDA adjudicated CLS events, of the 71 subjects with CLS, 6% of subjects required pressors for CLS, 4% required ventilator support, and 3% required dialysis.

Table 31. Full Safety Population – Subjects Requiring Intensified Interventions for CLS

Subject		CLS Grade	Disease	Dose (µg/kg/day)	Pressors	Ventilator support	Dialysis
STML-401-0114	(b) (6)	3	BPDCN	12	X		
STML-401-0114		4	BPDCN	12	X	X	
STML-401-0114		5	BPDCN	7	X	X	
STML-401-0114		5	BPDCN	12	X	X	
STML-401-0114		5	AML	16			X
STML-401-0114		E	AML	16			X

Source: FDA Analysis

Reviewer comment: CLS did not appear to be a dose-related toxicity as it occurred at all doses and dose schedules of tagraxofusp-erzs studied. Relying on the PT “capillary leak syndrome” reported in ADAE underestimated the incidence of CLS, especially low-grade events (all grades 19%, Grade ≥ 3 6%). In the Focused Safety Population, the overall incidence of composite CLS was 55% with Grade $\geq C$ CLS occurring in 9% of subjects. Most events occurred early in treatment, with 50% of subjects experiencing CLS in Cycle 1 and 9% in Cycle 2. Because most events were Grade A-B, few subjects required intervention beyond per protocol supportive care with albumin with or without diuretics or steroids. Within the Grade 3/C CLS events, only 1 subject required pressor support. It appears that with close monitoring and early intervention, most CLS events seen with tagraxofusp-erzs are manageable. Administration of

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Cycle 1 in the inpatient setting should further mitigate the risk. The prescribing information should clearly delineate management guidelines for CLS and should describe the commonly observed signs and symptoms.

Visual Acuity

Denileukin difitox is a recombinant IL-2–diphtheria toxin fusion protein approved in 1999 for the treatment of subjects with persistent or recurrent CD25-expressing cutaneous T-cell lymphoma. Boxed warnings for this drug include CLS and infusion related reactions (discussed above) and loss of visual acuity and color vision. The label notes that most subjects reported persistent visual impairment.

Adverse events of any grade visual impairment (grouped term) were reported at any time on study in 11/139 (8%) of subjects. The most frequently reported PT was “vision blurred” (n=7). Other terms were “visual impairment” (n=2) and “visual acuity reduced” (n=2). Fifty-six percent of the reported events occurred during Cycle 1, with 2 events each in Cycles 2 and 3, and 1 event each in Cycles 5 and 7. All events were Grade 1 except for one Grade 2 report of “visual acuity reduced”. Nine events are recorded as recovered/resolved in the ADAE data file. The remaining two events were reported by the Applicant as resolved in the Response to Clinical IR received 1 Nov 2018.

Reviewer comment: Persistent visual impairment was not seen in any subjects treated with tagraxofusp-erzs.

Veno-occlusive disease/SOS post-HSCT

Three out of 20 subjects with BPDCN who underwent SCT at any time after SL-401 treatment developed VOD.

One subject received SL-401 only prior to SCT:

- (b) (6) (first-line BPDCN) – best response of CRc. The subject received 6 cycles of SL-401 with a duration of exposure of 110 days, before being bridged to allogeneic SCT on Day +26 post SL-401. The subject was determined to have VOD 34 days post-SCT (diagnostic criteria not reported). Subject was alive at last follow-up (Day +89).

Two subjects received other therapy prior to SCT:

- (b) (6) (first-line BPDCN) – best response of PR on SL-401. The subject received 7 cycles of SL-401, with a duration of exposure of 138 days, before discontinuing due to PD. After SL-401 discontinuation, the subject received alternate therapy with hyper-CVAD and methotrexate on Day +10 through Day +33 post-SL-401 and then underwent allogeneic SCT on Day +74. The subject was determined to have VOD 45 days post-SCT (diagnostic criteria not reported). Subject was alive at last follow-up (Day +183)

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- (b) (6) (R/R BPDCN) – achieved a best response of CR, received 6 cycles of SL-401, with a duration of exposure of 117 days, before discontinuing because she elected to undergo SCT. After SL-401 discontinuation, the subject received alternate therapy with cyclophosphamide and underwent haploidentical peripheral SCT on Day 123 post SL-401. The subject was determined to have VOD 23 days post-SCT (Seattle criteria). The subject died due to multi-organ failure 69 days post-SCT.

Reviewer comment: Based on the above findings, there did not appear to be a higher risk for VOD post-HSCT in subjects who received tagraxofusp-erzs treatment.

Hypersensitivity

Forty-three of ninety-four (46%) subjects in the Focused Safety Population had at least one preferred term under SMQ hypersensitivity. Most were low-grade and included rash, pruritis, stomatitis, and wheezing in ≥ 5% of subjects. All PTs reported in more than one subject are shown in the table below.

Table 32. Focused Safety Population – SMQ Hypersensitivity PT

	All Grade		Grade ≥ 3	
	n	%	n	%
Pruritus	9	10%	0	0%
Rash	8	9%	1	1%
Stomatitis	7	7%	0	0%
Rash maculo-papular	7	7%	1	1%
Wheezing	5	5%	0	0%
Flushing	4	4%	0	0%
Erythema	4	4%	0	0%
Respiratory failure	4	4%	4	4%
Cytokine release syndrome	3	3%	1	1%
Rash macular	2	2%	0	0%
Swelling face	2	2%	0	0%
Drug eruption	2	2%	0	0%

Source: FDA Analysis

Reviewer comment: Events classified as hypersensitivity occurred in 46% of subjects including low-grade pruritis and rash. There is also some overlap between the subjects identified using this SMQ and those discussed above with capillary leak syndrome. The prescribing information should describe the commonly observed types of hypersensitivity events.

8.5. Supportive Safety Results

8.5.1. Common Treatment Emergent Adverse Events and Adverse Reactions

Common TEAEs of any grade and Grade ≥ 3 are shown in Tables 33 and 34 in the Full and Focused Safety Populations, respectively. The most common TEAEs were CLS signs and symptoms and elevated LFTs. Cytopenias and GI toxicities were also commonly reported.

Table 33. Full Safety Population – Common ($\geq 15\%$) TEAEs Any Grade and Grade ≥ 3

Preferred Term*	BPDCN N = 61		AML N = 49		MPN N = 29		Pooled N = 139	
	n	%	n	%	n	%	n	%
Any Grade TEAE	61	100%	49	100%	29	100%	139	100%
CLS signs/symptoms	52	85%	47	96%	27	93%	126	91%
Elevated LFTs	47	77%	36	73%	10	34%	93	67%
Nausea	28	46%	27	55%	14	48%	69	50%
Thrombocytopenia	28	46%	11	22%	10	34%	49	35%
Pyrexia	27	44%	22	45%	12	41%	61	44%
Fatigue	26	43%	28	57%	15	52%	69	50%
Arrhythmia	26	43%	19	39%	8	28%	53	38%
Hyperglycaemia	21	34%	17	35%	3	10%	41	29%
Chills	19	31%	12	24%	8	28%	39	28%
Anemia	16	26%	13	27%	12	41%	41	29%
Constipation	16	26%	10	20%	12	41%	38	27%
Neutropenia	15	25%	22	45%	16	55%	53	38%
Headache	15	25%	17	35%	10	34%	42	30%
Decreased appetite	14	23%	15	31%	10	34%	39	28%
Hypokalaemia	13	21%	13	27%	7	24%	33	24%
Back pain	13	21%	10	20%	8	28%	31	22%
Hypocalcaemia	13	21%	8	16%	3	10%	24	17%
Hyponatraemia	12	20%	7	14%	2	7%	21	15%
Vomiting	11	18%	15	31%	12	41%	38	27%
Dizziness	11	18%	12	24%	12	41%	35	25%
Anxiety	11	18%	5	10%	5	17%	21	15%
Hypertension	11	18%	5	10%	2	7%	18	13%
Tachycardia	10	16%	10	20%	4	14%	24	17%
Diarrhoea	9	15%	13	27%	10	34%	32	23%
Any Grade ≥ 3 TEAE	52	85%	43	88%	27	93%	122	88%
Elevated LFTs	31	51%	17	35%	1	3%	49	35%
Thrombocytopenia	23	38%	11	22%	8	28%	42	30%
Neutropenia	11	18%	18	37%	2	7%	31	22%

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CLS signs/symptoms	10	16%	10	20%	6	21%	26	19%
Anemia	9	15%	11	22%	10	34%	30	22%
Febrile neutropenia	5	8%	15	31%	1	3%	21	15%

*Includes Grouped Terms

Source: FDA Analysis

Table 34. Focused Safety Population – Common (≥ 15%) TEAEs Any Grade and Grade ≥ 3

Preferred Term*	BPDCN N = 58		AML N = 36		Pooled N = 94	
	n	%	n	%	n	%
Any Grade TEAE	58	100%	36	100%	94	100%
CLS signs/symptoms	49	84%	35	97%	84	89%
Elevated LFTs	44	76%	24	67%	68	72%
Nausea	27	47%	20	56%	47	50%
Pyrexia	26	45%	14	39%	40	43%
Thrombocytopenia	26	45%	7	19%	33	35%
Fatigue	25	43%	18	50%	43	46%
Arrhythmia	24	41%	14	39%	38	40%
Hyperglycaemia	20	34%	7	19%	27	29%
Chills	17	29%	10	28%	27	29%
Neutropenia	15	26%	17	47%	32	34%
Headache	15	26%	13	36%	28	30%
Anemia	15	26%	8	22%	23	24%
Constipation	15	26%	8	22%	23	24%
Decreased appetite	14	24%	10	28%	24	26%
Hypokalemia	13	22%	10	28%	23	24%
Back pain	13	22%	6	17%	19	20%
Anxiety	11	19%	4	11%	15	16%
Hypertension	11	19%	3	8%	14	15%
Vomiting	10	17%	11	31%	21	22%
Dizziness	10	17%	9	25%	19	20%
Hypocalcaemia	10	17%	4	11%	14	15%
Hyponatraemia	10	17%	4	11%	14	15%
Diarrhoea	9	16%	10	28%	19	20%
Insomnia	9	16%	7	19%	16	17%
Hyperphosphatemia	9	16%	1	3%	10	11%
Dyspnoea	7	12%	11	31%	18	19%
Febrile neutropenia	6	10%	13	36%	19	20%
Cough	4	7%	10	28%	14	15%
Haematuria	3	5%	6	17%	9	10%

Any Grade ≥ 3 TEAE	49	84%	30	83%	79	84%
Elevated LFTs	29	50%	10	28%	39	41%
Thrombocytopenia	21	36%	7	19%	28	30%
Neutropenia	11	19%	14	39%	25	27%
CLS signs/symptoms	9	16%	6	17%	15	16%
Anemia	8	14%	6	17%	14	15%
Febrile neutropenia	5	9%	12	33%	17	18%

*Includes Grouped Terms

Source: FDA Analysis

As discussed in Section 4.5, the high levels of ADA significantly decrease the exposure to drug after Cycle 2. However, in the absence of progressive disease or transplantation, tagraxofusp-erzs is given indefinitely, so FDA looked at the safety profile by cycle in the Focused Safety Population (Tables 35 and 36).

Table 35. Focused Safety Population – Common ($\geq 15\%$) TEAEs by Cycle

Preferred Term*	BPDCN		AML		Pooled	
	n	%	n	%	n	%
Cycle 1	N = 58		N = 36		N = 94	
CLS signs/symptoms	45	78%	33	92%	78	83%
Elevated LFTs	41	71%	11	31%	52	55%
Thrombocytopenia	25	43%	7	19%	32	34%
Nausea	21	36%	19	53%	40	43%
Fatigue	21	36%	14	39%	35	37%
Pyrexia	21	36%	9	25%	30	32%
Hyperglycaemia	15	26%	7	19%	22	23%
Chills	14	24%	8	22%	22	23%
Anemia	14	24%	8	22%	22	23%
Arrhythmia	13	22%	10	28%	23	24%
Headache	12	21%	11	31%	23	24%
Hypokalemia	12	21%	5	14%	17	18%
Constipation	11	19%	7	19%	18	19%
Neutropenia	10	17%	15	42%	25	27%
Decreased appetite	10	17%	8	22%	18	19%
Hyponatraemia	9	16%	4	11%	13	14%
Hypocalcaemia	9	16%	3	8%	12	13%
Hyperphosphatemia	9	16%	0	0%	9	10%
Dizziness	6	10%	8	22%	14	15%
Insomnia	6	10%	7	19%	13	14%
Dyspnea	5	9%	10	28%	15	16%

Febrile neutropenia	4	7%	12	33%	16	17%
Diarrhea	3	5%	6	17%	9	10%
Cough	1	2%	8	22%	9	10%
Cycle 2	N = 52		N = 49		N = 101	
CLS signs/symptoms	19	37%	8	16%	27	27%
Elevated LFTs	9	17%	8	16%	17	17%
Cycle ≥ 3	N = 41		N = 4		N = 45	
CLS signs/symptoms	20	49%	2	50%	22	49%
Arrhythmia	10	24%	1	25%	11	24%

*Includes Grouped Terms

Source: FDA Analysis

Table 36. Focused Safety Population – Common (≥ 10%) Grade ≥ 3 TEAEs by Cycle

Preferred Term*	BPDCN		AML		Pooled	
	n	%	n	%	n	%
Cycle 1	N = 58		N = 36		N = 94	
Elevated LFTs	27	47%	10	28%	37	39%
Thrombocytopenia	20	34%	7	19%	27	29%
Neutropenia	9	16%	13	36%	22	23%
Anemia	8	14%	6	17%	14	15%
CLS signs/symptoms	6	10%	5	14%	11	12%
Hyponatraemia	6	10%	1	3%	7	7%
Febrile neutropenia	4	7%	11	31%	15	16%
Cycle 2	N = 52		N = 49		N = 101	
None						
Cycle ≥ 3	N = 41		N = 4		N = 45	
None						

*Includes Grouped Terms

Source: FDA Analysis

In Cycle 2 and beyond no Grade ≥ 3 adverse events were reported in more than 5% of subjects. In Cycle 2, the most common Grade ≥ 3 adverse events in the pooled population were elevated LFTs (5%) and CLS signs/symptoms (5%). In Cycles 3 and beyond, the most common Grade ≥ 3 adverse events reported in the pooled population was hypertension (5%).

Reviewer comment: There is a notable reduction in the incidence of adverse events, especially Grade ≥ 3 events, observed in later cycles of treatment which corresponds to the drop in drug exposure due to the presence of ADA. Subjects continuing on treatment with tagraxofusp-erzs beyond 2 cycles do not appear to be at high risk for added toxicity from the additional exposure.

8.5.2. Laboratory Findings

Common shifts in laboratory abnormalities are shown in Table 37. More subjects with AML had baseline levels of hematologic toxicity, and those who were not had higher incidences of treatment-emergent thrombocytopenia and anemia. Subjects with BPDCN appeared to have higher incidences of hepatic toxicities.

Table 37. Focused Safety Population – Selected Laboratory Value Shifts

Laboratory Abnormality	BPDCN		AML		Pooled	
	Baseline Grade ≤2 n (%)	Grade ≥3 at least once n (%)	Baseline Grade ≤2 n (%)	Grade ≥3 at least once n (%)	Baseline Grade ≤2 n (%)	Grade ≥3 at least once n (%)
Hematologic toxicity						
• Thrombocytopenia	45	26 (58%)	9	8 (89%)	54	34 (63%)
• Neutropenia	45	20 (44%)	11	4 (36%)	56	24 (43%)
• Anemia	53	15 (28%)	24	18 (75%)	77	33 (43%)
Hepatic toxicity						
• AST increased	58	25 (43%)	36	10 (28%)	94	35 (37%)
• ALT increased	58	20 (34%)	36	8 (22%)	94	28 (30%)
• Hyperbilirubinemia	58	0 (0%)	36	0 (0%)	93	0 (0%)
Renal toxicity						
• Creatinine	58	0 (0%)	36	0 (0%)	94	0 (0%)
Other						
• Hyperglycemia	58	14 (24%)	35	5 (14%)	93	19 (20%)

Source: FDA Analysis based on ADLB

Abbreviations: ALT – alanine aminotransferase; AST – aspartate aminotransferase

Reviewer comment: Because the incidence of AEs in Cycle 3 and beyond is low (Section 8.5.1) and the PK data suggests that the level of exposure after Cycle 2 is small (Section 4.5), the remainder of the safety review will concentrate on toxicities in the Focused Safety Population in Cycles 1 and 2.

Renal Toxicity

Renal toxicity was observed in the nonclinical toxicology studies (see Section 4.4) and was the cause of death in cynomolgus monkeys at the highest doses tested.

In clinical trials, as seen in Table 37 above, no subjects in the Focused Safety Population experienced a shift to Grade 3 or greater creatinine increases based on the ADLB data file.

Widening the search to the full safety population, one 60-year old subject with MPN treated at the 12 mcg/kg/day dose (3-day dosing schedule) had a creatinine > 5x ULN (Grade 3) on Day 19 (STML-401-0314- (b) (6)). This subject had documented CLS that resolved a week before the elevated creatinine, but the narrative describes only a concurrent Grade 3 right atrial thrombus on Day 19. The subsequent creatinine value in ADLB on Day 27 has decreased to within normal limits.

Grading of creatinine increases in ADLB are based on fold-increases over the upper limit of normal. However, creatinine increases of > 3x baseline also meet the definition of Grade 3 toxicity. Applying this definition to the full safety population identified one 58-year old subject with AML treated at the 16 µg/kg/day dose who had an increase in creatinine to > 3x baseline on Days 4 and 5 in the setting of FDA adjudicated possible CLS (see death narrative for STML-401-0114 (b) (6)).

Additional analyses were performed on the ADAE data file by high level term (HLT):

- HLT: Renal function analyses – 11/94 (12%) subjects in the pooled Focused Safety Population (BPDCN: 12%, AML: 11%) had a preferred term of blood creatinine increased and/or glomerular filtration rate decreased during Cycle 1. No subjects had a Grade ≥ 3 event reported.
- HLT: Renal failure and impairment – 6% of the pooled population (BPDCN: 5, AML: 1) had a preferred term of acute kidney injury (AKI) or renal failure in Cycle 1, and one subject (BPDCN) had a Grade 3 AKI in the setting of CLS.

Two subjects in the full safety population required dialysis in the setting of CLS. No other subjects were reported to have required dialysis.

Reviewer comment: Given these analyses, high grade renal toxicity does not appear to be strongly correlated with treatment with tagraxofusp-erzs in the absence of capillary leak syndrome.

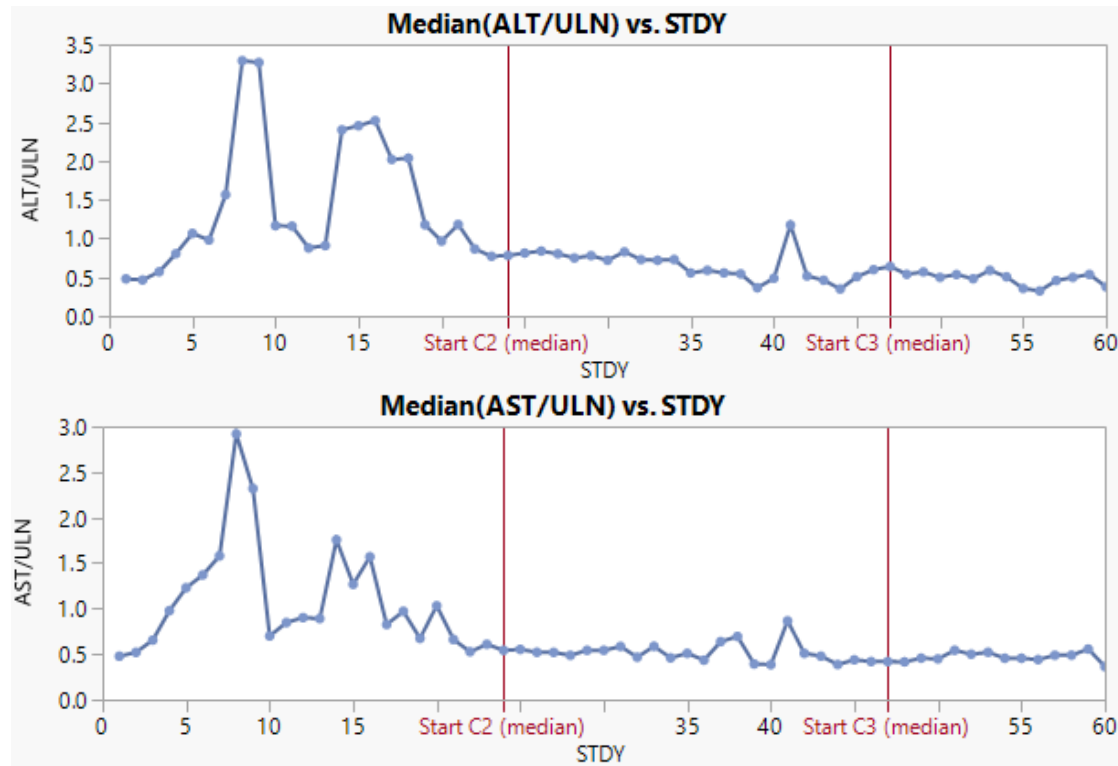
Hepatotoxicity

Elevated LFTs

Elevated LFTs were the second most commonly reported TEAEs (Table 34) after CLS signs and symptoms. Eighteen subjects (19%) in the focused safety population had at least one dose delayed due to elevated LFTs. As shown above in Table 37, all subjects had baseline AST and ALT ≤ Grade 1 and 37% and 30%, respectively, experienced a shift to Grade ≥ 3 at least once. Most cases were transient and resolved with drug interruption or without intervention (i.e. events occurring after treatment had been completed for that cycle).

Figure 4 shows that these increases were most significant during Cycle 1. Both AST and ALT elevations appeared to a peak between Days 7-10 followed by a second peak between Days 14-19 before stabilizing at the start of Cycle 2. Data are shown normalized to the upper limit of normal for the laboratory measurement.

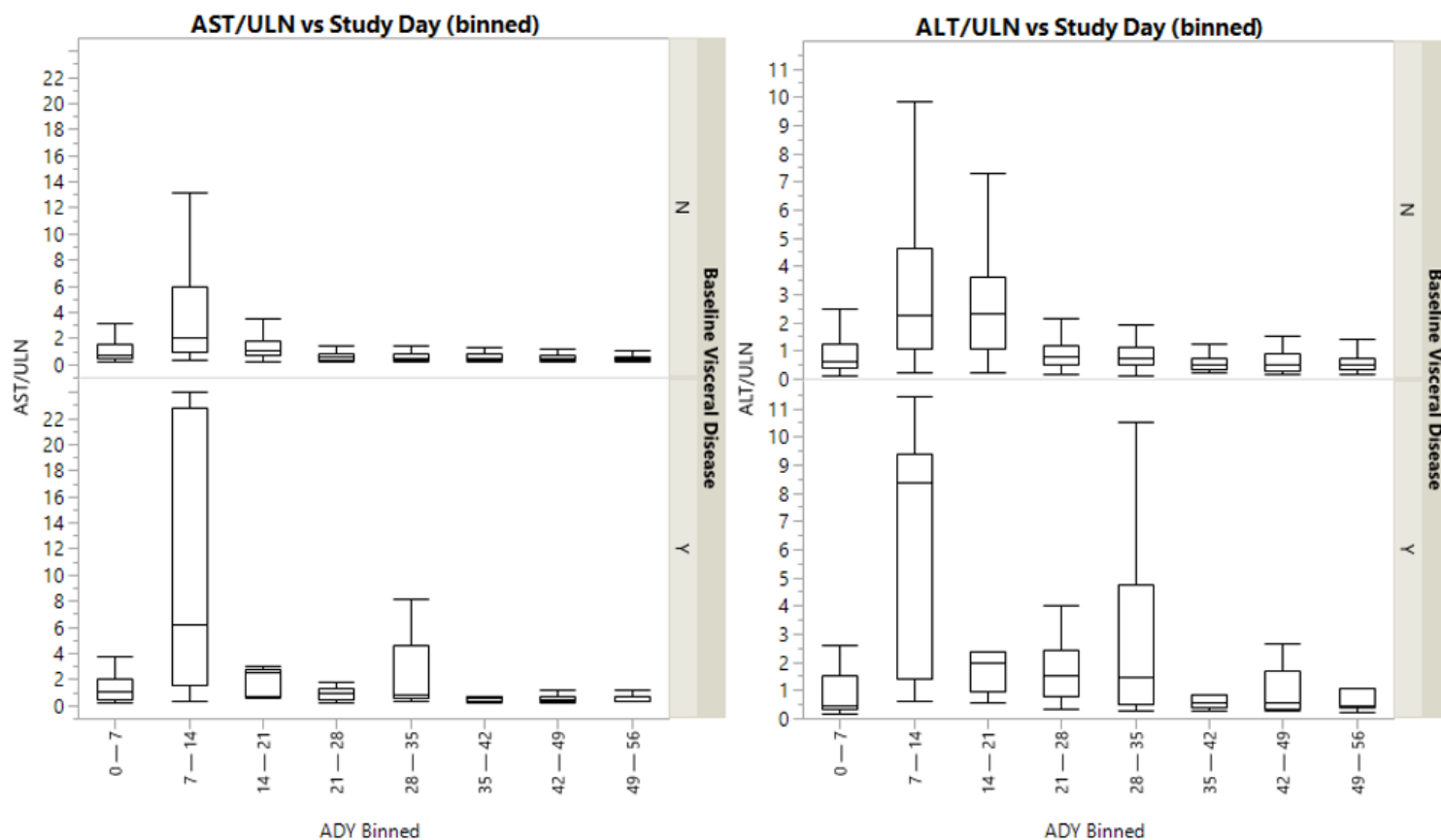
Figure 4. Focused Safety Population – AST and ALT Time Trends



Source: FDA Analysis

As noted in Table 37, subjects with BPDCN appeared to have a higher incidence of elevated AST and ALT. One possible reason for the higher incidence of elevated LFTs in subjects with BPDCN was the presence of baseline visceral disease which may have involved the liver. Figure 5 shows that subjects with baseline visceral disease had higher severity AST and ALT elevations Days 7-14 than those without visceral disease. Furthermore, they appeared to have a second smaller peak Days 28-35 (Cycle 2) which was not seen in the absence of baseline visceral disease.

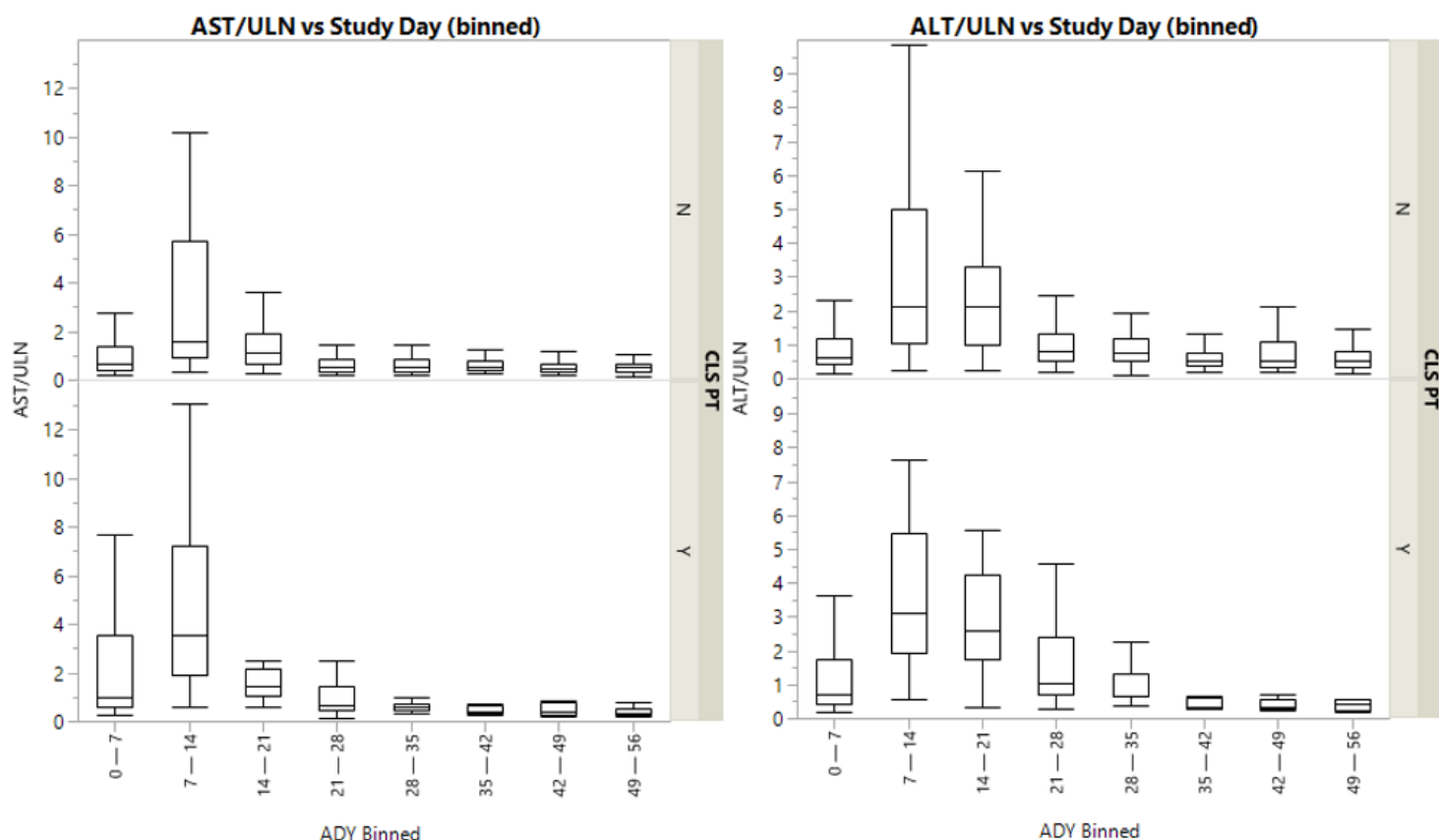
Figure 5. Focused Safety Population – AST and ALT in Subjects With and Without Baseline Visceral Disease



Source: FDA Analysis

FDA also looked at the possible contribution of CLS to elevated transaminases. Although both median AST and ALT (normalized to ULN) were nominally higher on Days 7-14 in subjects who had CLS (by preferred term) (Figure 6), the small number of subjects makes it difficult to conclude that the subjects with CLS had higher severity AST/ALT elevations. A similar analysis using FDA Composite CLS (not shown) also showed nominally higher median AST/ALT elevations on Days 7-14 in subjects with composite CLS but with considerable overlap in range. The hepatotoxicity observed in Cycle 1 cannot be solely explained by CLS.

Figure 6. Focused Safety Population – AST and ALT in Subjects With and Without Grade ≥ 3 CLS



Source: FDA Analysis

Potential Hy's Law Cases

Two subjects met the criteria for Hy's Law, 1 based on the ALT and bilirubin criteria (STML-401-0114-^{(b) (6)}), and 1 based on AST and bilirubin criteria (STML-401-0114-^{(b) (6)}). Neither case was considered by the applicant to represent DILI due to concurrent evidence of progression or ongoing toxicities that can themselves cause liver function abnormalities. Brief narrative summaries for these 2 subjects follow:

STML-401-0114-^{(b) (6)} – 31yo male not previously treated for BPDCN with no extramedullary disease involvement or hepatobiliary history. A summary of his LFT values in Cycle 1 is shown below. One day after the 3rd infusion in Cycle 1, he developed an ALT $\geq 3 \times$ ULN. Concomitant medications included acetaminophen and levofloxacin as well as amphetamine, dextroamphetamine, ondansetron, docusate senna, Phenergan, pseudoephedrine, loratadine pseudoephedrine, sodium chloride, ibuprofen, magnesium oxide/magnesium sulfate, zinc sulfate, omega-3 fatty acids, and vitamin A. He subsequently received infusions 4 and 5. His ALT fluctuated and on Day 15 increased to $> 4 \times$ ULN. On Day 21, 9 days after the last dose of

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tagraxofusp-erzs, his ALT had dropped to 57 (slightly elevated) but he had an elevated bilirubin > 2x ULN with normal ALP. No associated clinical events were reported. On Day 26, both ALT and bilirubin were back within normal limits. There were no subsequent reports of elevated ALT through his last dose Cycle 7 infusion 1 after which he discontinued due to progressive disease.

Parameter	BL	C1Inf1	C1Inf2	C1Inf3	1 Day Post-C1Inf3	C1Inf4	C1Inf5	C1D8	C1D15	C1D21
ALT (U/L)	24	23	22	26	141	136	113	135	174	57
AST (U/L)	31	29	24	27	122	100	61	63	55	28
Bilirubin (μmol/L)	12.0	12.0	15.4	8.6	10.3	13.7	12.0	12.0	25.7	46.2
ALP (U/L)	55	54	53	58	71	68	65	60	57	50

Reviewer comment: *This subject's ALT elevation corresponds with the trend seen in the overall safety population and was trending downward by the time his bilirubin peaked. Both ALT and bilirubin elevations had resolved at the next measured lab after day 21. Acetaminophen and levofloxacin could potentially contribute to the liver toxicity.*

STML-401-0114- (b) (6) – 82yo male not treated previously for BPDCN with no extramedullary disease involvement in the liver and no hepatobiliary history. A summary of his LFT values in Cycle 1 is shown below. He received all infusions in Cycle 1. By Day 8, his AST had increased to 6x ULN while his bilirubin remained normal and ALP slightly elevated. On Day 9, he was diagnosed with CLS with prolonged hospitalization. Concomitant medications included acetaminophen as well as levofloxacin, ondansetron, tigecycline, furosemide, metolazone, metoprolol tartrate, valacyclovir, caspofungin, cefpodoxime, proxetil, naproxen, acetylsalicylic acid, simvastatin, cefepime, chondroitin with glucosamine, sertraline, Sinemet, glyceryl trinitrate, and albumin. The subject died as a result of CLS 2 weeks after his last dose.

Parameter	BL	C1Inf1	C1Inf2	C1Inf3	C1Inf4	C1Inf5	C1D8	C1D15
AST (U/L)	24	-	25	26	73	94	276	492
ALT (U/L)	12	16	13	20	12	25	49	127
Bilirubin (μmol/L)	10.3	12.0	8.6	8.6	8.6	6.8	10.3	123.1
ALP (U/L)	85	77	69	67	62	62	119	-

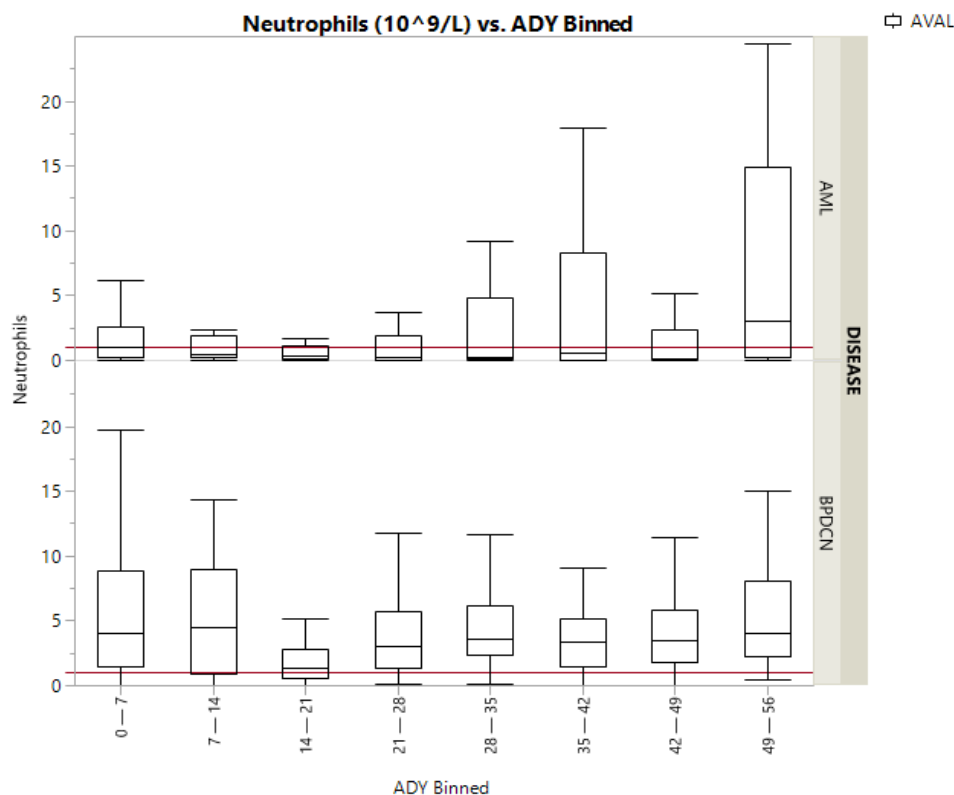
Reviewer comment: *Hepatotoxicity is commonly seen in the setting of CLS. In this subject, the elevated ALT and bilirubin can be attributed to concurrent CLS.*

Reviewer comment: Hepatotoxicity is common after treatment with tagraxofusp-erzs, especially during Cycle 1. Subjects with baseline visceral disease were noted to have had more severe AST and ALT elevations along with a second, milder round of hepatotoxicity in Cycle 2 not generally seen in subjects without visceral disease. However, most cases were transient and resolved either with drug interruption (if occurring during the treatment portion of the cycle) or without intervention. No firm conclusions could be drawn regarding the contribution of CLS to the severity of hepatotoxicity. Drug-induced liver injury is not anticipated.

Hematologic Toxicities

Although neutropenia was seen in the focused safety population, Figure 7 shows that a majority of the neutropenia occurred in subjects with AML. In contrast, subjects with BPDCN were less likely to be severely neutropenic at baseline and experienced only a brief drop in neutrophil count on Days 14-21 with recovery soon thereafter.

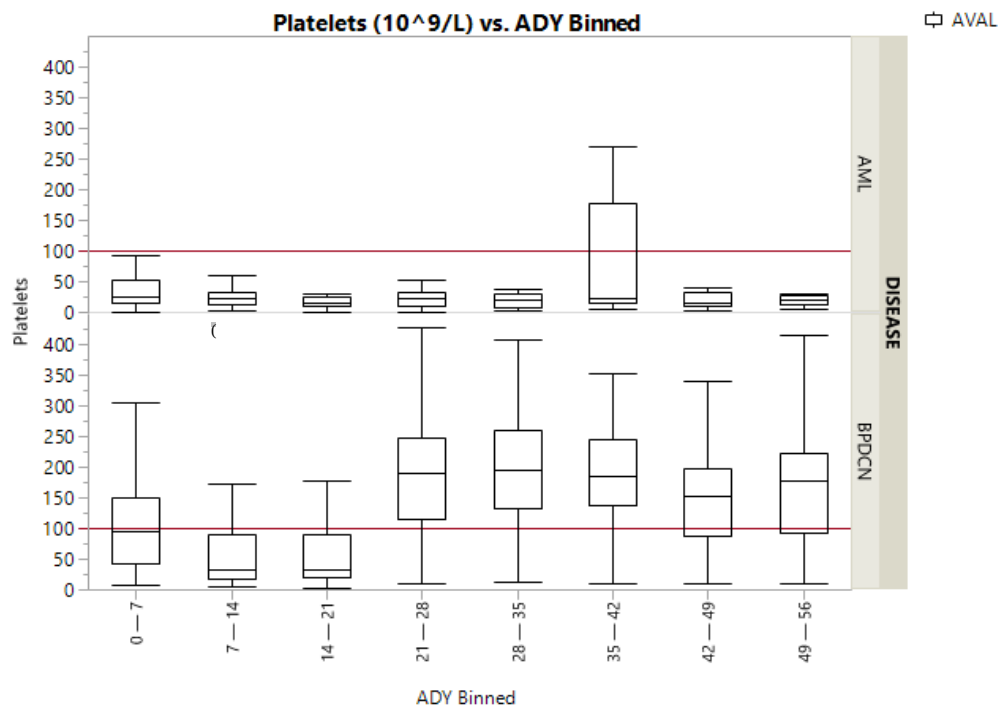
Figure 7. Focused Safety Population – Neutrophil Count in Cycles 1 and 2



Source: FDA Analysis

Thrombocytopenia was seen in the focused safety population. Figure 8 shows that, in subjects with BPDCN, a drop in platelet count was seen on Days 7-21 with recovery soon thereafter.

Figure 8. Focused Safety Population – Platelet Count in Cycles 1 and 2



Source: FDA Analysis

Reviewer comments: In subjects with BPDcN, there is a brief window of mild neutropenia during the third week of Cycle 1 which recovers before the end of the cycle. The incidence of febrile neutropenia was 7% during this time period and there were no reports of sepsis. Tagraxofusp-erzs had a greater effect on the duration and severity of thrombocytopenia, particularly in weeks 2 and 3 of Cycle 1, but did not cause prolonged thrombocytopenia as most subjects had platelet count recovery in week 4. In subjects with BPDcN, there were 4 (7%) bleeding events of any grade and no Grade ≥ 3 bleeding events.

8.5.3. Vital Signs

The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters. The most common AEs (≥ 5%) were tachycardia [HR >120 bpm] (22%), hypotension [SBP <90 mmHg with decrease ≥20 mmHg and/or DBP <50 mmHg with decrease ≥10 mmHg] (17%), and hypertension [SBP >180 mmHg and increase ≥20 mmHg] (6%). No apparent dose relationship was seen with regard to change from baseline in vital signs.

Reviewer comments: Both hypotension and tachycardia are commonly seen with capillary leak syndrome.

8.5.1. **Electrocardiograms (ECGs)**

Section 4.2.1 of the Summary of Clinical Safety (Module 2.4.7) reports:
“Neither acute nor chronic treatment with tagraxofusp-erzs was associated with consistent changes in any of the ECG variables of HR, PR, QRS, or QTcF. In particular the 90% upper confidence limit for the baseline-adjusted Fridericia-corrected QT interval (Δ QTcF) was below the threshold of regulatory concern (~20 msec) on ECGs recorded 30 minutes and 60 minutes after infusions on 4 different infusion days in BPDCN subjects (Study 0114, Table 14.3.5.10A).”

The QT-IRT review noted that “in the QT study, five (5%) subjects had ECG QT prolonged reported as a TEAE, including 3 BPDCN subjects (6%) and 2 AML subjects (4%), all of whom received SL-401 at 12 μ g/kg/day. All 3 BPDCN subjects had at least 1 QTcF interval >500 ms. None of these 5 subjects experienced syncope or presyncope or had a cardiac TEAE. No cases were considered serious or led to treatment discontinuation.

No subject experienced Torsade de pointes during the study.

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

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

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

These findings are consistent with those reported for the focused safety population (Table 38).

Table 38. Focused Safety Population – ECG-related Preferred Terms Reported in $\geq$ 2 Subjects

	BPDCN N = 58	AML N = 36
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Preferred Term	n	%	n	%
Tachycardia	9	16	7	19
Atrial fibrillation	4	7	0	0
Bradycardia	4	7	1	3
Electrocardiogram QT prolonged	4	7	2	6
Sinus tachycardia	2	3	2	6
Sinus bradycardia	2	3	4	11

Source: FDA Analysis

8.5.2. QTc

Section 4.2.3 of the Summary of Clinical Safety (Module 2.4.7) reports that “a QTc/exposure analysis was performed using data from 95 subjects in Study 0114 to evaluate the relationship between tagraxofusp-erzs concentrations and duration of the QTcF and the duration of the RR interval and whether ADA alter the relationships between tagraxofusp-erzs concentration and ECG metrics. Findings revealed no significant QT prolongation effect with tagraxofusp-erzs, and neutralizing antibodies did not show any apparent impact on relationships between tagraxofusp-erzs concentration and ECG endpoints.”

Table 39. STML-401-0114 – ECG Summary of PR, QRS, and QTcF by Disease

Electrocardiogram Categorical Summary of PR, QRS, and QTcF: By Disease
(Safety Population)

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

Source: STML-401-0114 CSR, Table 14.3.5.11A

The QT-IRT review notes that their review of the data yielded similar results, and that no large QTc prolongation effect (i.e., > 20 ms) of tagraxofusp-erzs (12 µg/kg/day x 5 days every 21 days) was observed, consistent with tagraxofusp-erzs being a large protein and therefore having a

low likelihood of direct ion channel interaction. The clinical data do not suggest any off-target effects for QTc prolongation. As a large protein, tagraxofusp-erzs has low likelihood of direct ion channel interactions and no concentration-QTc analyses were recommended.

8.5.3. Immunogenicity

The clinical pharmacology review noted:

“In 130 patients treated with tagraxofusp-erzs in 4 clinical trials:

- 96% (115/120) of patients evaluable for the presence of pre-existing ADA at baseline before treatment were confirmed positive with 21% being positive for the presence of neutralizing antibodies. The high prevalence of ADA 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 of tagraxofusp-erzs.
- 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 of tagraxofusp-erzs.”

Table 40. STML-401-0114 – Impact of Anti-tagraxofusp-erzs Neutralizing Antibody on Efficacy and Safety

	FL BPDCN (N = 25)		R/R BPDCN (N = 13)		
	Baseline NAB+ Post-trt NAB+ (n = 6)	Baseline NAB- Post-trt NAB+ (n = 19)	Baseline NAB+ Post-trt NAB+ (n = 3)	Baseline NAB- Post-trt NAB+ (n = 8)	Baseline NAB- Post-trt NAB- (n = 2)
Doses Received	18 [2, 35]	28 [18, 180]	10 [10, 23]	18 [8, 35]	6 [5, 7]
CR+CRc % [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: FDA Clinical Pharmacology Analysis, Midcycle

Reviewer comment: As discussed in Section 4.5, the high rate of pre-existing and treatment emergent ADAs had a significant impact on the PK of tagraxofusp-erzs, with drug exposure markedly reduced by Cycle 3 and many patients having measurements below the limit of quantification of the assay. It appears from Table 40 that subjects who were baseline

neutralizing antibody negative may have had higher rates of CR/CRc and higher rates of Grade ≥ 3 TEAEs. This makes intuitive sense, but the small patient numbers in each column make it impossible to draw any firm conclusions (large overlap in confidence intervals). The median time to CR/CRc was within 2 cycles. However, tagraxofusp-erzs is potent at levels well below the lower level of quantification of the assay and most of the toxicity was also seen in the first two cycles of therapy (when drug exposure was higher). Therefore, there is no evidence to support restricting treatment to two cycles.

8.6. Analysis of Submission-Specific Safety Issues

8.7. Other Safety Explorations

8.7.1. Dose Dependency for Adverse Events

Toxicities of tagraxofusp-erzs by dose on 5-day schedule

There are little safety data for other doses of tagraxofusp-erzs given on the 5-day schedule. In general, the safety profile was similar to that seen in subjects treated with the 12 $\mu\text{g}/\text{kg}/\text{day}$ dose described in Table 41. The most common TEAEs of any grade were CLS signs and symptoms and elevated LFTs. Common Grade ≥ 3 TEAEs occurring in 2 or more subjects at any dose level are presented below.

Table 41. STML-401-0114 – Grade ≥ 3 TEAEs within 30 Days of Follow-up by Tagraxofusp-erzs Dose Given on 5-day Schedule

Preferred Term*	7 $\mu\text{g}/\text{kg}/\text{day}$ N = 6		9 $\mu\text{g}/\text{kg}/\text{day}$ N = 3		16 $\mu\text{g}/\text{kg}/\text{day}$ N = 7	
	n	%	n	%	n	%
Any Grade ≥ 3 TEAE	6	100%	3	100%	7	100%
Elevated LFTs	4	67%	1	33%	4	57%
Anemia	2	33%	0	0%	4	57%
CLS signs/symptoms	1	17%	0	0%	4	57%
Thrombocytopenia	3	50%	0	0%	3	43%
Neutropenia	1	17%	1	33%	2	29%
Acute kidney injury	0	0%	0	0%	2	29%
Hepatic failure	0	0%	0	0%	2	29%
Respiratory failure	0	0%	0	0%	2	29%
Lymphopenia	3	50%	0	0%	0	0%

Source: FDA Analysis

Toxicities of tagraxofusp-erzs by dose schedule

The most significant differences in TEAEs between the 5-day and 3-day regimens of 12 µg/kg/day were higher incidences of any grade CLS signs/symptoms and elevated LFTs in the 5-day regimen group. Table 42 below shows common Grade ≥ 3 TEAEs in Cycle 1 in subjects treated with 12 µg/kg/day of tagraxofusp-erzs on a 5-day vs 3-day regimen. The most significant difference in Grade ≥ 3 TEAEs was the higher incidence of elevated LFTs in the 5-day regimen group.

Table 42. Common (>20%) Grade ≥ 3 TEAEs in Cycle 1 – 12 µg/kg/day: 5 vs 3-day Regimens

Preferred Term*	5-day Regimen (BPDCN/AML) N = 94		3-day Regimen (MPN) N = 36	
	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%

Source: FDA Analysis

Grade ≥ 3 CLS signs/symptoms occurred in 12% of subjects in the 5-day group compared with 8% in the 3-day group.

Renal function:

- HLT: Renal function analyses – 11/94 (12%) subjects on the 5-day regimen had an event reported compared with 4/36 (17%) subjects on the 3-day regimen in Cycle 1. No subjects had a Grade ≥ 3 event reported.
- HLT: Renal failure and impairment – 5/94 (6%) subjects on the 5-day regimen had an event reported compared with 4/36 (17%) subjects on the 3-day regimen in Cycle 1.
- One subject in each group had a Grade ≥ 3 event of AKI, 1 reported previously with CLS (5-day) and 1 without a narrative (3-day).

Reviewer comments: Although it appears that subjects treated at 16 µg/kg/day may have had a higher incidence of high grade elevated LFTs and CLS signs/symptoms than those treated at lower doses on the 5-day schedule, given the small number of subjects treated at each dose level a clear relationship between AE severity and dose cannot be established.

With regards to 5-day vs 3-day dosing schedules, the incidence of high-grade in LFT elevations was higher in subjects on the 5-day schedule. There was a less substantial difference in the incidence of high-grade CLS signs/symptoms, and there did not appear to be a difference in renal toxicity.

8.7.2. Safety Analyses by Demographic Subgroups

The overall toxicity profile of tagraxofusp-erzs was similar in patients age ≥ 75 years with the exception of a higher incidence of encephalopathy (grouped term) (Table 43). The most common preferred terms in the ≥ 75 years group were confusional state (n=7), mental status changes (n= 4), and encephalopathy, lethargy, and somnolence (1 each). In the <75 years group, the terms reported were confusional state (n=4) and somnolence (n=2).

Table 43. Focused Safety Population – Grade ≥ 3 TEAEs within 30 Days of Follow-up by Age ≥ 75 vs < 75 Years

Preferred Term*	≥ 75 years old N = 22		< 75 years old N = 72		Pooled N = 94	
	n	%	n	%	n	%
Any Grade TEAE	22	100%	72	100%	94	100%
CLS signs/symptoms	21	95%	63	89%	84	89%
Elevated LFTs	15	68%	53	74%	68	72%
Arrhythmia	11	50%	27	38%	38	40%
Nausea	10	45%	37	51%	47	50%
Encephalopathy	10	45%	4	6%	14	15%
Hyperglycaemia	9	41%	25	16%	27	29%
Pyrexia	8	36%	32	44%	40	43%
Thrombocytopenia	8	36%	25	35%	33	35%
Anemia	8	36%	15	21%	23	24%
Constipation	8	36%	15	21%	23	24%
Chills	7	32%	20	28%	27	29%
Neutropenia	6	27%	26	36%	32	34%
Blood creatinine	6	27%	7	10%	23	24%
Any Grade ≥ 3 TEAE					79	84%
Elevated LFTs	12	55%	27	38%	39	41%
Thrombocytopenia	8	36%	20	28%	28	30%
CLS signs/symptoms	6	27%	9	13%	15	16%
Anemia	6	27%	8	11%	14	15%
Neutropenia	5	23%	20	28%	25	27%

*Includes Grouped Terms
Source: FDA Analysis

Table 44. Focused Safety Population – Selected Laboratory Value Shifts by Age ≥ 75 vs < 75 Years

	Age ≥ 75 Years	Age < 75 Years
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Laboratory Abnormality	Baseline Grade ≤2 n (%)	Grade ≥3 at least once n (%)	Baseline Grade ≤2 n (%)	Grade ≥3 at least once n (%)
Hematologic toxicity				
• Thrombocytopenia	13	10 (77%)	41	24 (59%)
• Neutropenia	12	5 (42%)	44	19 (43%)
• Anemia	18	7 (39%)	60	27 (45%)
Hepatic toxicity				
• AST increased	22	10 (45%)	73	26 (36%)
• ALT increased	22	7 (32%)	73	21 (29%)
• Hyperbilirubinemia	22	0	72	0
Renal toxicity				
• Creatinine	22	0	73	0
Other				
• Hyperglycemia	22	5 (23%)	72	15 (21%)

Source: FDA Analysis

Abbreviations: ALT – alanine aminotransferase; AST – aspartate aminotransferase

Renal function:

- HLT: Renal function analyses – 6/22 (7%) subjects ≥ 75 years of age had an event reported compared with 7/72 (10%) subjects < 75 years of age. No subjects had a Grade ≥ 3 event reported.
- HLT: Renal failure and impairment – 3/22 (14%) subjects ≥ 75 years of age had an event reported compared with 6/72 (8%) subjects < 75 years of age. Only one subject had a Grade ≥ 3 event of AKI which was reported in the setting of CLS.

Reviewer comment: No conclusions can be drawn based on a single-arm trial on whether subjects ≥75 years of age are generally more prone to encephalopathy (or more prone to toxicity in general) or if this is a drug-specific adverse reaction to which these subjects are more sensitive. However, there is an objectively higher rate of encephalopathy in subjects ≥75 years of age (risk difference 40%); it may be prudent to include this observation in the prescribing information. Renal and hepatic toxicity did not appear to be significantly higher in subjects ≥75 years of age.

8.8. Specific Safety Studies/Clinical Trials

No other trials were conducted to evaluate specific safety concerns.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

Eight neoplasms were identified in 8 subjects in the safety database, including 4 subjects in the BPDCN subgroup. Subjects were between the ages of 61 and 80 and were treated with varying doses of tagraxofusp-erzs. Six of the subjects were still undergoing treatment with tagraxofusp-erzs when the neoplasm was documented; the remaining 2 subjects were 2 and 6 days from their last dose.

One basal cell carcinoma was recorded on study day 1. Median time to report for the remainder of the neoplasms was day 57 (range 12-346). The neoplasms reported were basaloid neoplasm (neck), squamous cell carcinoma (neck), renal cell carcinoma, bladder urothelial carcinoma, verrucoid keratosis, metastatic melanoma, and seborrheic keratoses. None of the neoplasms were considered by the investigator to be related to study drug.

8.9.2. Human Reproduction and Pregnancy

There are no data on the effects of tagraxofusp-erzs in subjects who are pregnant or nursing.

8.9.3. Pediatrics and Assessment of Effects on Growth

Tagraxofusp-erzs received orphan designation for the treatment of BPDCN on 6/6/13. Therefore, this application is exempt from the requirement for a pediatric assessment.

(b) (4)
Further descriptions of these subjects are reported in the publication by Sun, et al. 2018.

The 3 pediatric subjects were ages 10, 12, and 15 years. All 3 had positive CD123 expression in their tumors. Two received tagraxofusp-erzs for relapsed/refractory BPDCN and one as front-line therapy for BPDCN (parental choice). All three subjects were treated with 12 µg/kg/day x 5 days, and they received 2-5 cycles.

One subject experienced Grade 3 febrile neutropenia and catheter-related infection, and Grade 4 lymphopenia. No other Grade 3 or higher AEs were reported in any patient.

The most frequently described Grade 1-2 AEs were similar to those reported in adults in Section 8.5.1. These included CLS signs and symptoms (weight gain (n=3), hypoalbuminemia, hypotension, limb edema, periorbital edema – one each) and elevated LFTs (n=2). Gastrointestinal disturbances (nausea, vomiting) were reported in 2 subjects.

Reviewer comments: No new safety signals were identified in the pediatric population. Given

the small sample size and lack of detailed efficacy data, no conclusions can be drawn regarding efficacy. But, tagraxofusp-erzs is a targeted therapy, and pediatric BPDCN tumor cells express CD123. There is no biological reason to expect that pediatric BPDCN would respond differently to tagraxofusp-erzs compared with adult BPDCN, and there is no compelling reason not to extend the indication to include pediatric patients 2 years and older.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the Full Safety Population, 7 subjects received tagraxofusp-erzs at a dose of 16 µg/kg/day. Although the subject numbers are small, the TEAE profile for those subjects was similar to that at a dose of 12 µg/kg/day. No TEAE occurred at a dose of 16 µg/kg/day that had not also occurred at lower doses of ≤ 12 µg/kg/day. No subjects received >10% of the prescribed dose.

8.9.5. Other Safety Populations

Additional safety data were provided from STML-401-0214 of 16 subjects with AML in complete remission who received tagraxofusp-erzs at doses of 7, 9, or 12 µg/kg/day x 5 days as maintenance therapy. No new safety signals were identified in this population.

Additional safety data were provided from STML-401-0414 of 7 subjects with multiple myeloma treated with tagraxofusp-erzs 7 µg/kg/day in combination with pomalidomide and dexamethasone. Only one death was reported which occurred 179 days after EOT in a subject who discontinued due to disease progression. No new safety signals were identified in this population.

8.9.6. Safety Concerns Identified Through Postmarket Experience

Tagraxofusp-erzs is not marketed in any country, and there is no postmarket experience.

8.9.7. Expectations on Safety in the Postmarket Setting

Overall safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. However, it is recognized that post-approval use of tagraxofusp-erzs will not be limited to those with adequate organ function and performance status that was required for enrollment on the clinical trials. Therefore, safety in the postmarket setting is not entirely predictable.

8.9.8. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

The primary data in support of safety for the proposed indication came from STML-401-0114 in which 94 subjects (58 with BPDCN and 36 with R/R AML) were exposed to tagraxofusp-erzs at 12 µg/kg/day on Days 1-5 of a 21-day cycle. Data from an additional 45 subjects exposed to other doses or dose schedules of tagraxofusp-erzs were included in the integrated safety database and supported the safety review.

Fatal toxicities occurred in 2/94 (2%) of subjects in the Focused Safety Population. Early mortality was relatively low. Sixty-day mortality was 15% among all patients in the Focused Safety Population and 5% among patients with BPDCN. This compares favorably with the morbidity and mortality seen with intensive chemotherapy regimens.

Common AEs resulting in treatment delay or discontinuation were CLS signs and symptoms and elevated LFTs. Common AEs (> 30%) overall in the study included signs and symptoms of CLS, elevated transaminases, nausea, pyrexia, fatigue, thrombocytopenia, and neutropenia. The incidence of cytopenias was higher in the AML population than in the BPDCN population. In subjects with BPDCN, both neutropenia and thrombocytopenia resolved within 1 cycle and there were no associated reports of significant sepsis or bleeding.

Capillary leak syndrome was the only fatal toxicity seen with tagraxofusp-erzs in the focused safety population. Relying on the PT “capillary leak syndrome” reported in ADAE underestimated the incidence of CLS, especially low-grade events (all grades 19%, Grade ≥ 3 6%). The incidence of composite CLS was 55% with Grade ≥ C CLS occurring in 9% of subjects. Most events occurred early in treatment, with 50% of subjects experiencing CLS in Cycle 1 and 9% in Cycle 2. The first cycle of tagraxofusp-erzs therapy was administered in the inpatient setting, and, in general, toxicities were manageable with monitoring and early intervention, including albumin and diuretics. Transient hepatotoxicity was commonly seen in subjects treated with tagraxofusp-erzs. Most elevated transaminases occurred during Cycle 1 and resolved without intervention or with temporary interruption of drug.

The overall toxicity profile of tagraxofusp-erzs was similar in patients age ≥ 75 years with the exception of a higher incidence of encephalopathy (grouped term). The most commonly reported preferred terms were “confusional state” and “altered mental status.” No conclusions can be drawn based on a single-arm trial on whether subjects ≥75 years of age are generally more prone to encephalopathy (or more prone to toxicity in general) or if this is a drug-specific adverse reaction to which these subjects are more sensitive. Renal and hepatic toxicity did not appear to be significantly higher in subjects ≥75 years of age.

Safety data were available for 3 pediatric subjects ages 10, 12, and 15 years with BPDCN treated with tagraxofusp-erzs at the labeled dose and schedule. No new safety signals were identified

in the pediatric population. Given the small sample size and lack of detailed efficacy data, no conclusions can be drawn regarding efficacy. But, tagraxofusp-erzs is a targeted therapy, and pediatric BPDCN tumor cells express CD123. There is no biological reason to expect that pediatric BPDCN would respond differently to tagraxofusp-erzs compared with adult BPDCN.

As discussed in Section 4.5, the high rate of pre-existing and treatment emergent ADAs had a significant impact on the PK of tagraxofusp-erzs, with drug exposure markedly reduced by Cycle 3 and many patients having measurements below the limit of quantification of the assay. On STML-401-0114, the median time to CR/CRc was within 2 cycles, but treatment continued indefinitely in the absence of progressive disease. However, tagraxofusp-erzs is potent at levels well below the lower level of quantification of the assay and most of the toxicity was also seen in the first two cycles of therapy (when drug exposure was higher). Therefore, there is no evidence to support restricting treatment to two cycles.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

- **Highlights:** Add boxed warning for capillary leak syndrome
- **1 Indications and Usage:** extend the indication to include pediatric subjects ages 2 years and older
- **2 Dosage Modification:** include management guidelines for CLS and monitoring guidelines for renal and hepatic function
- **5.1 Warnings and Precautions:** Capillary leak syndrome – (b) (4)
[REDACTED]
- **6 Adverse Reactions:** revise table to reflect the Focused Safety Population described in this review. Add table of common laboratory abnormalities.
- **8.4 Pediatric Use:** update to include safety in pediatric subjects and extrapolation of efficacy from adults
- **8.5 Geriatric Use:** updated to include the observed higher incidence of encephalopathy reported in subjects ages ≥ 75 years

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- **14 Clinical Studies:**

(b) (4)

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

None.

The primary concern with this drug is capillary leak syndrome which appears to be manageable with monitoring and early intervention. The first cycle of treatment is administered in the inpatient setting during which subjects can be closely monitored. The label includes a conservative management strategy to help mitigate the risks of CLS.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): STML-401-0114

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>9 investigators, 49 subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>49</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Grouped Terms Used for Adverse Reactions

Table 45. Grouped Terms Used for Adverse Reactions

Grouped Term	Preferred Terms Included In Grouped Term
Abdominal pain	Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
Altered state of consciousness	Altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, stupor
Anemia	Anaemia, erythropenia, haematocrit decreased, haemoglobin decreased, red blood cell count decreased
Anxiety	Adjustment disorder with anxiety, anxiety, anxiety disorder, generalised anxiety disorder
Arrhythmia	Arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia, bradycardia, heart rate irregular, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular, tachyarrhythmia, supraventricular tachycardia, tachycardia, ventricular extrasystoles, ventricular fibrillation, ventricular tachyarrhythmia, ventricular tachycardia
Cytokine release syndrome/infusion reaction	Cytokine release syndrome, cytokine storm, capillary leak syndrome, infusion related reaction, macrophage activation
CRS signs/symptoms	Ascites, Capillary leak syndrome, Cytokine release syndrome, Dyspnoea, Eyelid oedema, Face oedema, Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Hypoalbuminaemia, Hypotension, Hypovolaemia, Infusion related reaction, Laryngeal oedema, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Peripheral swelling, Pulmonary oedema, Swelling, Swelling face, Tongue oedema, Weight increased
Delirium	Delirium, delirium febrile
Depression	Depressed mood, depression, depression suicidal, major depression, completed suicide, suicide attempt, adjustment disorder with depressed mood, adjustment disorder with mixed anxiety and depression, agitated depression, Columbia suicide severity rating abnormal, suicidal ideation, suicidal behavior
Device issue	Device dislocation, device issue, device leakage, device occlusion, medical device complication

Grouped Term	Preferred Terms Included In Grouped Term
Diarrhea	Colitis, diarrhoea, diarrhoea haemorrhagic, diarrhoea infectious, enteritis, enterocolitis, gastroenteritis, gastroenteritis viral, neutropenic colitis, viral diarrhoea
Dysphasia	Aphasia, dysarthria
Dyspnea	Acute respiratory distress syndrome, acute respiratory failure, bronchial hyperreactivity, bronchospasm, dyspnoea, dyspnoea at rest, dyspnoea exertional, respiratory distress, respiratory failure, respiratory rate increased, tachypnoea, wheezing
Edema	Face oedema, fluid retention, generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling face
Encephalopathy	Encephalopathy, toxic encephalopathy
Elevated liver function tests	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, Hypertransaminasemia, liver function test increased, transaminases increased
Fungal infection	Abscess fungal, aspergillus infection, bronchopulmonary aspergillosis, cerebral aspergillosis, fungal infection, fungal skin infection, gastrointestinal candidiasis, gastrointestinal fungal infection, hepatic candidiasis, hepatic infection fungal, oral fungal infection, respiratory moniliasis, respiratory tract infection fungal, splenic infection fungal, systemic candida
GGT increase	Gamma-glutamyltransferase abnormal, gamma-glutamyltransferase increased
GI hemorrhage	Anal haemorrhage, duodenal ulcer haemorrhage, duodenal ulcer perforation, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haemorrhoidal haemorrhage, intestinal haemorrhage, large intestinal haemorrhage, lower gastrointestinal haemorrhage, melaena, oesophageal haemorrhage, rectal haemorrhage, small intestinal haemorrhage, upper gastrointestinal haemorrhage
GVHD	Acute graft versus host disease, acute graft versus host disease in intestine, acute graft versus host disease in liver, acute graft versus host disease in skin, chronic graft versus host disease, chronic graft versus host disease in intestine, chronic graft versus host disease in liver, chronic graft versus host disease in skin, graft versus host disease, graft versus host disease in eye, graft versus host disease in gastrointestinal tract, graft versus host disease in liver, graft versus host disease in lung, graft versus host disease in skin
Headache	Cluster headache, headache, sinus headache, tension headache

Grouped Term	Preferred Terms Included In Grouped Term
Hearing impaired	Deafness, deafness bilateral, deafness permanent, deafness transitory, deafness unilateral, hearing disability, hearing impaired, sudden hearing loss
Hematuria	Cystitis haemorrhagic, haematuria
Hepatotoxicity	Acute hepatic failure, chronic hepatic failure, hepatic failure, hepatocellular injury, hepatotoxicity, subacute hepatic failure
Hyperbilirubinemia	Bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice
Hyperglycemia	Blood glucose increased, diabetes mellitus, glucose tolerance impaired, hyperglycaemia
Hypersensitivity	Anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, hypersensitivity, urticaria
Hypertransaminitis	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hypertransaminasemia, transaminases increased
Hypotension	Blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, circulatory collapse, hypotension, hypovolemic shock
Hypogammaglobulinemia	Blood immunoglobulin A decreased, blood immunoglobulin D decreased, blood immunoglobulin E decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased
Intracranial hemorrhage	Central nervous system haemorrhage, cerebellar haemorrhage, cerebral haemorrhage, haemorrhage intracranial, hemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, subdural haemorrhage
Injection site reaction	Injection site inflammation, infusion site irritation, infusion site oedema, infusion site swelling, infusion site warmth, injection site erythema, injection site extravasation, injection site haematoma, injection site oedema, injection site reaction, injection site swelling
Leukopenia	Leukopenia, white blood cell count decreased
Medication error	Accidental overdose, device use error, dose calculation error, drug administration error, drug dispensing error, drug titration error, intentional overdose, medication error, overdose, prescribed overdose, product preparation error
Myocardial infarction	Acute myocardial infarction, myocardial infarction

Grouped Term	Preferred Terms Included In Grouped Term
Mucositis	Glossitis, mouth haemorrhage, mucosal inflammation, pharyngeal inflammation, stomatitis
Neurotoxicity	Neurological decompensation, neurological symptom, neurotoxicity
Neutropenia	Agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil count decreased
Pancreatitis	Haemorrhagic necrotic pancreatitis, pancreatitis, pancreatitis acute pancreatitis chronic, pancreatitis haemorrhagic
Paresis	Facial asymmetry, facial paresis, muscular weakness
Pericardial effusion	Cardiac tamponade, pericardial effusion
Peripheral neuropathy	Numb chin syndrome, peripheral sensory neuropathy
Phlebitis	Phlebitis, phlebitis infection, phlebitis superficial, thrombophlebitis
Pneumonia	Atypical pneumonia, interstitial lung disease, lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, lung infection pseudomonal, lung infiltration, organising pneumonia, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia necrotising, pneumonia pneumococcal, pneumonia staphylococcal, pneumonia streptococcal, pneumonia viral, pneumonitis, respiratory syncytial virus infection, respiratory tract infection
Pruritis	Pruritis, pruritis generalised
Pyrexia	Pyrexia, body temperature increased
Rash	Dermatitis, dermatitis contact, dermatitis exfoliative, drug eruption, eczema, erythema, exfoliative rash, palmar erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash vesicular, skin exfoliation, skin reaction, skin toxicity, toxic skin eruption
Renal impairment	Acute kidney injury, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate decreased, renal disorder, renal failure, renal impairment
Seizure	Atonic seizures, partial seizures, partial seizures with secondary generalization, seizure, simple partial seizures
Sepsis	Abdominal sepsis, bacteremia, bacterial sepsis, candida sepsis, device related sepsis, enterococcal sepsis, Enterobacter sepsis, Escherichia sepsis, fungal sepsis, neutropenic sepsis, post-

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Grouped Term	Preferred Terms Included In Grouped Term
	procedural sepsis, pulmonary sepsis, sepsis, sepsis syndrome, septic shock, viral sepsis
Thrombocytopenia	Platelet count decreased, thrombocytopenia
Thrombosis	Axillary vein thrombosis, cerebral venous thrombosis, deep vein thrombosis, embolism, embolism venous, hepatic vacuolar thrombosis, hepatic vein thrombosis, intracranial venous sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, ophthalmic vein thrombosis, ovarian vein thrombosis, pelvic venous thrombosis, penile vein thrombosis, portal vein thrombosis, pulmonary embolism, pulmonary venous thrombosis, pulmonary thrombosis, renal vein thrombosis, retinal vein thrombosis, splenic vein thrombosis, subclavian vein thrombosis, venous thrombosis, venous thrombosis limb
Transfusion reaction	Acute haemolytic transfusion reaction, allergic transfusion reaction, anaphylactic transfusion reaction, delayed haemolytic transfusions reaction, delayed serologic transfusion reaction, febrile non-hemolytic transfusion reaction, hemolytic transfusion reaction, transfusion reaction
Tremor	Action tremor, essential tremor, intention tremor, resting tremor, tremor
Visual impairment	Blindness, blindness unilateral, sudden visual loss, vision blurred, visual acuity reduced, visual impairment

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/s/

EMILY Y JEN
11/23/2018

DONNA PRZEPIORKA
11/23/2018

The secondary reviewer comments are incorporated in the CDTL review.