WARNING: CAPILLARY LEAK SYNDROME

Capillary Leak Syndrome (CLS) which may be life-threatening or fatal can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended *[see Warnings and Precautions (7.1)]*.

1. NAME OF THE MEDICINAL PRODUCT

ELZONRIS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 1 mg tagraxofusp. Each vial contains 1.15 mg of tagraxofusp.

Excipient with known effect. Each vial contains 50 mg of sorbitol.

For the full list of excipients, see section 11.

Patient Safety Information Card
The marketing of ELZONRIS is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

Prescriber guide
This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear colorless solution in a single-dose vial. A few white to translucent particles may be present.

4 THERAPEUTIC INDICATION

ELZONRIS is a CD123-directed cytotoxin for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults.

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

- Administer ELZONRIS at 12 mcg/kg intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. Continue treatment with ELZONRIS until disease progression or unacceptable toxicity. The dose is calculated based on the patient's actual weight.
- Prior to the first dose of the first cycle, ensure serum albumin is greater than or equal to 3.2 g/dL before administering ELZONRIS.
- Premedicate patients with an H1-histamine antagonist (e.g., diphenhydramine hydrochloride), H2-histamine antagonist (e.g., famotidine), corticosteroid (e.g., 50 mg intravenous methylprednisolone or

equivalent) and acetaminophen (or paracetamol) approximately 60 minutes prior to each ELZONRIS infusion.
- Administer Cycle 1 of ELZONRIS in the inpatient setting with patient observation through at least 24 hours after the last infusion.
- Administer subsequent cycles of ELZONRIS in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped with appropriate monitoring for patients with hematopoietic malignancies undergoing treatment. Observe patients for a minimum of 4 hours following each infusion.

5.2 Dosage Modifications

Monitor vital signs and check albumin, transaminases, and creatinine prior to preparing each dose of ELZONRIS. See Table 1 for recommended dose modifications and Table 2Table 2 for CLS management guidelines.

Table 1. Recommended ELZONRIS Dosage Modifications

Parameter	Severity Criteria	Dosage Modification
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Table 2)
Body weight	Body weight increase ≥ 1.5 kg over pretreatment weight on prior treatment day	See CLS Management Guidelines (Table 2Table 2)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold ELZONRIS until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold ELZONRIS until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold ELZONRIS until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold ELZONRIS until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	Withhold ELZONRIS until body temperature is < 38°C.
Hypersensitivity reactions	Mild or moderate	Withhold ELZONRIS until resolution of any mild or moderate hypersensitivity reaction. Resume ELZONRIS at the same infusion rate.
	Severe or life-threatening	Discontinue ELZONRIS permanently.

Table 2. CLS Management Guidelines

Time of Presentation	CLS Sign/Symptom	Recommended Action	ELZONRIS Dosing Management
Prior to first dose of ELZONRIS in cycle 1	Serum albumin < 3.2 g/dL	Administer ELZONRIS when serum albumin ≥ 3.2 g/dL.	
	Serum albumin < 3.5 g/dL		

During ELZONRIS dosing	Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle	Administer 25g intravenous albumin (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.	Interrupt ELZONRIS dosing until the relevant CLS sign/symptom has resolved[1].
	A predose body weight that is increased by ≥ 1.5 kg over the previous day's predose weight	Administer 25g intravenous albumin (q12h or more frequently as practical), and manage fluid status as indicated clinically (e.g., generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive), until body weight increase has resolved (i.e., the increase is no longer ≥ 1.5 kg greater than the previous day's predose weight).	
	Edema, fluid overload and/or hypotension	Administer 25g intravenous albumin (q12h, or more frequently as practical) until serum albumin is ≥ 3.5 g/dL. Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS sign/symptom or as indicated clinically. Aggressive management of fluid status and hypotension if present, which could include intravenous fluids and/or diuretics or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.	

[1] If ELZONRIS dose is held:

- ELZONRIS administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat hemodynamic instability
- ELZONRIS administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (e.g., required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved), and
- ELZONRIS administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.

5.3 Preparation for Administration

Assure the following components required for dose preparation and administration are available prior to thawing ELZONRIS:

- One infusion syringe pump
- One empty 10 mL sterile vial
- 0.9% Sodium Chloride Solution for Injection
- Three 10 mL sterile syringes
- One 1 mL sterile syringe
- One mini-bifuse Y-connector or equivalent
- Microbore tubing
- One 0.2 micron polyethersulfone in-line filter

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Thawed ELZONRIS appearance should be a clear, colorless liquid that may contain a few white to translucent particles.
- Prior to dose preparation allow vials to thaw at 25 °C or below for up to 1 hour in the outer carton, and verify thaw visually. Thawed vials may be held at room temperature for approximately 1 hour prior to dosage preparation. Do not force thaw. Do not refreeze vial once thawed.
- Use aseptic technique for preparation of the ELZONRIS dose.
- A 2-step process is required for preparation of the final ELZONRIS dose:
    - Step 1 - Prepare 10 mL of 100 mcg/mL ELZONRIS
        - Using a sterile 10 mL syringe, transfer 9 mL of 0.9% Sodium Chloride Solution for Injection to an empty sterile 10 mL vial.
        - Gently swirl the ELZONRIS vial to mix the contents, remove the cap, and using a sterile 1 mL syringe, withdraw 1 mL of thawed ELZONRIS from the product vial.
        - Transfer the 1 mL of ELZONRIS into the 10 mL vial containing the 0.9% Sodium Chloride Solution for Injection. Gently invert the vial at least 3 times to mix the contents. Do not shake vigorously.
        - Following dilution the final concentration of ELZONRIS is 100 mcg/mL.
    - Step 2 – Prepare the ELZONRIS infusion set.
        - Calculate the required volume of diluted ELZONRIS (100 mcg/mL) according to patient's weight.
        - Draw up the required volume into a new syringe (if more than 10 mL of diluted ELZONRIS (100 mcg/mL) is required for the calculated patient dose, repeat step 1 with a second vial of ELZONRIS). Label the ELZONRIS syringe.
        - Prepare a separate syringe with at least 3 mL of 0.9% Sodium Chloride Solution for Injection to be used to flush the administration set once the ELZONRIS dose is delivered.
        - Label the 0.9% Sodium Chloride Solution for Injection flush syringe.
        - Connect the 0.9% Sodium Chloride Solution for Injection flush syringe to one arm of the Y-connector or equivalent and ensure the clamp is closed.
        - Connect the product syringe to the other arm of the Y-connector or equivalent and ensure the clamp is closed.
        - Connect the terminal end of the Y-connector or equivalent to the microbore tubing.
        - Remove the cap from the supply side of the 0.2 micron filter and attach it to the terminal end of the microbore tubing.
        - Unclamp the arm of the Y-connector or equivalent connected to the 0.9% Sodium Chloride Solution for Injection flush syringe. Prime the Y-connector or equivalent up to the intersection (do not prime the full infusion set with 0.9% Sodium Chloride Solution for Injection). Re-clamp the Y-connector or equivalent line on the 0.9% Sodium Chloride Solution for Injection flush arm.
        - Remove the cap on the terminal end of the 0.2 micron filter and set it aside. Unclamp the arm of the Y-connector or equivalent connected to the product syringe, and prime the entire infusion set, including the filter. Recap the filter, and re-clamp the Y-connector or equivalent line on the product side. The infusion set is now ready for delivery for dose administration.
- Administer ELZONRIS within 4 hours. During this 4-hour window, the prepared dose should remain at 25 °C.

- Do not reuse excess ELZONRIS. Any excess material should be thrown away immediately following infusion.

5.4 Administration

- Establish venous access and maintain with sterile 0.9% Sodium Chloride Solution for Injection.
- Administer the prepared ELZONRIS dose via infusion syringe pump over 15 minutes. The total infusion time will be controlled using a syringe pump to deliver the entire dose and the 0.9% Sodium Chloride Solution for Injection flush over 15 minutes.
- Insert the ELZONRIS syringe into the syringe pump, open the clamp on the ELZONRIS side of the Y-connector or equivalent and deliver the prepared ELZONRIS dose.
- Once the ELZONRIS syringe has been emptied, remove it from the pump and place the 0.9% Sodium Chloride Solution for Injection flush syringe in the syringe pump.
- Open the clamp on the 0.9% Sodium Chloride Solution for Injection flush side of the Y-connector or equivalent and resume infusion via the syringe pump at the pre-specified flow to push remaining ELZONRIS dose out of the infusion line to complete delivery.

6 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

7 WARNINGS AND PRECAUTIONS

7.1 Capillary Leak Syndrome

Capillary leak syndrome (CLS), including life-threatening and fatal cases, has been reported among patients treated with ELZONRIS. In patients receiving ELZONRIS in clinical trials, the overall incidence of CLS was 53% (65/122), including Grade 1 or 2 in 43% (52/122) of patients, Grade 3 in 7% (8/122) of patients, Grade 4 in 1% (1/122) of patients, and four fatalities (3%) *[see Adverse reactions (9.1)]*. The median time to onset was 4 days (range - 1 to 46 days), and all but 5 patients experienced an event in Cycle 1.

Before initiating therapy with ELZONRIS, ensure that the patient has adequate cardiac function and serum albumin is greater than or equal to 3.2 g/dL. During treatment with ELZONRIS, monitor serum albumin levels prior to the initiation of each dose of ELZONRIS and as indicated clinically thereafter, and assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema, including pulmonary edema, hypotension or hemodynamic instability *[see Dosage and Administration (5.2)]*.

7.2 Hypersensitivity Reactions

ELZONRIS can cause severe hypersensitivity reactions. In patients receiving ELZONRIS in clinical trials, hypersensitivity reactions were reported in 43% (53/122) of patients treated with ELZONRIS and were Grade ≥ 3 in 7% (9/122) *[see Adverse reactions (9.1)]*. Manifestations of hypersensitivity reported in ≥ 5% of patients include rash, pruritus, and stomatitis. Monitor patients for hypersensitivity reactions during treatment with ELZONRIS. Interrupt ELZONRIS infusion and provide supportive care as needed if a hypersensitivity reaction should occur. In case of severe or life-threatening hypersensitivity reactions discontinue ELZONRIS permanently *[see Dosage and Administration (5.2)].*

7.3 Hepatotoxicity

Treatment with ELZONRIS was associated with elevations in liver enzymes. In patients receiving ELZONRIS in clinical trials, elevations in ALT occurred in 79% (96/122) and elevations in AST occurred in 76% (93/122) *[see Adverse reactions (9.1)]*. Grade 3 ALT elevations were reported in 26% (32/122) of patients. Grade 3 AST elevations were reported in 30% (36/122) and Grade 4 AST elevations were reported in 3% (4/122) of patients. Elevated liver enzymes occurred in the majority of patients in Cycle 1 and were reversible following dose interruption.

Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) prior to each infusion with ELZONRIS. Withhold ELZONRIS temporarily if the transaminases rise to greater than 5 times the upper limit of normal and resume treatment upon normalization or when resolved *[see Dosage and Administration (5.2)].*

7.4 Tumour Lysis Syndrome

ELZONRIS can cause tumour lysis syndrome (TLS), which may be fatal as a result of its rapid anti-tumour activity. Identify TLS based on clinical presentation and symptoms, including acute renal failure, hyperkalaemia, hypocalcaemia, hyperuricaemia, or hyperphosphataemia from tumour lysis. Patients considered at high risk for TLS due to high tumour burden should be managed as clinically indicated, including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care.

8 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ELZONRIS has no or negligible influence on the ability to drive or use machines.

9 ADVERSE REACTIONS

The following serious adverse drug reactions are described elsewhere in the labeling:

- Capillary Leak Syndrome *[see Warnings and Precautions (7.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (7.2)]*
- Hepatotoxity *[see Warnings and Precautions (7.3)]*
- Tumour Lysis Syndrome *[see Warnings and Precautions (7.4)]*

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety of ELZONRIS was assessed in a single-arm clinical trial that included 122 adults with newly diagnosed or relapsed/refractory myeloid malignancies, including 86 with BPDCN, treated with ELZONRIS 12 mcg/kg daily for 5 days of a 21-day cycle. The overall median number of cycles started was 2.5 (range, 1-76), and 4 in patients with BPDCN (range, 1-76).

Four (3%) patients (4/122) had fatal adverse reactions, all of which were related to capillary leak syndrome. Overall, 8% (10/122) of patients discontinued treatment with ELZONRIS due to an adverse reaction; the most common adverse reactions resulting in treatment discontinuation were hepatic toxicities, hypoalbuminemia and CLS (2% each).

Table 3 summarizes the common (≥ 10%) adverse reactions with ELZONRIS in patients with myeloid malignancies. The rate of any given adverse reaction or lab abnormality was derived from all the reported events of that type.

Table 3. Adverse Reactions in ≥ 10% of Patients Receiving 12 mcg/kg of ELZONRIS

	N=122	
	All Grades %	**Grade ≥ 3 %**
Vascular Disorders		
Capillary leak syndrome[1]	53	11
Hypotension	25	7

	N=122	
	All Grades %	**Grade ≥ 3 %**
Hypertension	14	6
General disorders and administration site conditions		
Fatigue	45	7
Pyrexia	43	0
Peripheral edema	39	1
Chills	26	1
Gastrointestinal disorders		
Nausea	45	0
Constipation	24	0
Diarrhea	21	0
Vomiting	19	0
Investigations		
Weight increase	31	0
Nervous system disorders		
Headache	28	0
Dizziness	21	0
Metabolism and nutrition disorders		
Decreased appetite	22	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	20	3
Epistaxis	12	1
Cough	12	0
Blood and lymphatic system disorders		
Febrile neutropenia	19	16
Musculoskeletal and connective tissue disorders		
Back pain	19	2
Pain in extremity	10	2
Cardiac disorders		
Tachycardia	17	0
Psychiatric disorders		
Insomnia	16	0
Anxiety	15	0
Skin and subcutaneous tissue disorders		
Pruritus	10	0

[1] Capillary leak syndrome defined as any event reported as CLS during treatment with ELZONRIS or the occurrence of at least 2 of the following CLS manifestations within 7 days of each other:

hypoalbuminemia (including albumin value less than 3.0 g/dL), edema (including weight increase of 5 kg or more), hypotension (including systolic blood pressure less than 90 mmHg).

Clinically relevant adverse reactions occurring in less than 10% of patients treated with ELZONRIS included tumour lysis syndrome.

Table 4 summarizes the clinically important laboratory abnormalities that occurred in ≥ 10% patients with myeloid malignancies treated with ELZONRIS.

Table 4. Selected Laboratory Abnormalities in Patients Receiving 12 mcg/kg of ELZONRIS

	Treatment-Emergent Laboratory Abnormalities	
	All Grades %	**Grade ≥ 3 %**
Hematology		
Platelets decrease	68	49
Hemoglobin decrease	61	30
Neutrophils decrease	38	29
Chemistry		
Glucose increase	89	21
ALT increase	79	26
AST increase	76	33
Albumin decrease	72	1
Calcium decrease	57	2
Sodium decrease	52	9
Potassium decrease	36	6
Phosphate decrease	32	10
Creatinine increase	26	0
Magnesium decrease	25	0
Alkaline phosphatase increase	22	1
Potassium increase	20	3
Magnesium increase	13	4
Bilirubin increase	11	0
Glucose decrease	10	0

Report of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary
Based on its mechanism of action, ELZONRIS has the potential for adverse effects on embryo-fetal development *[see Clinical Pharmacology (12.1)].* There are no available data on ELZONRIS use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Animal reproduction or developmental toxicity studies have not been conducted with tagraxofusp. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes.

10.2 Lactation

Risk Summary
No data are available regarding the presence of ELZONRIS in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from ELZONRIS, breast feeding is not recommended during treatment and for 1 week after the last dose.

10.3 Females and Males of Reproductive Potential

Based on its mechanism of action, ELZONRIS may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)].*

Pregnancy Testing:
Conduct pregnancy testing in females of reproductive potential within 7 days prior to initiating ELZONRIS treatment.

Contraception:
Advise females to use acceptable contraceptive methods during ELZONRIS treatment and for 1 week after the last dose of ELZONRIS.

10.4 Pediatric Use

ELZONRIS is not indicated for children and adolescents below the age of 18 years.
There is limited information on the safety and efficacy of ELZONRIS in children and adolescents below the age of 18 years.

10.5 Geriatric Use

Of the 86 patients who received ELZONRIS for BPDCN at the labeled dose in STML-401-0114, 63% were 65 years and older and 22% were 75 years and older. Patients 75 years or older experienced a higher incidence of altered mental status (including confusional state, delirium, mental status changes, dementia, and encephalopathy) than patients under 75 years of age.

11 DESCRIPTION

Tagraxofusp, a CD123-directed cytotoxin, is a fusion protein comprised of a recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT). Tagraxofusp has an approximate molecular weight of 57,695 Daltons. Tagraxofusp is constructed by recombinant DNA technology and produced in *Escherichia coli* cells.

ELZONRIS (tagraxofusp) injection is a preservative-free, sterile, clear, colorless solution that may contain a few white to translucent particles and requires dilution prior to intravenous infusion. ELZONRIS is supplied at a concentration of 1 mg/mL in a single-dose vial. Each mL of ELZONRIS contains 1 mg tagraxofusp, sorbitol (50.0 mg), sodium chloride (4.383 mg), tromethamine base (Tris) buffer (2.422 mg) and Water for Injection and pH is 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tagraxofusp is a CD123-directed cytotoxin composed of recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) fusion protein that inhibits protein synthesis and causes cell death in CD123-expressing cells.

ATC code: L01XX67

12.2 Pharmacodynamics

The exposure-response relationships and the time course of pharmacodynamic response for ELZONRIS have not been fully characterized.

12.3 Pharmacokinetics

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

Distribution

Mean (SD) volume of distribution of tagraxofusp is 5.1 (1.9) L in patients with BPDCN.

Elimination

Mean (SD) clearance is 7.1 (7.2) L/hr in patients with BPDCN. Mean (SD) terminal half-life of tagraxofusp is 0.7 (0.3) hours.

Specific Population

No clinically significant differences in the pharmacokinetics of tagraxofusp were observed based on age (22 to 84 years), sex, mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2, estimated by MDRD), mild (total bilirubin ≤ ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment or body weight after adjusting dose by body weight. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), or severe hepatic impairment (total bilirubin >3 times ULN and any AST) on tagraxofusp pharmacokinetics is unknown.

Drug Interaction Studies

No drug-drug interaction studies have been conducted with ELZONRIS.

12.4 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELZONRIS with the incidences of antibodies to other products may be misleading. Immune response to ELZONRIS was evaluated by assessment of serum binding reactivity against ELZONRIS (anti-drug antibodies; ADA) and neutralizing antibodies by inhibition of functional activity. Immune response to ELZONRIS was assessed using two immunoassays. The first assay detected reactivity directed against ELZONRIS (ADA), and the second assay detected reactivity against

the interleukin-3 (IL-3) portion of ELZONRIS. Two cell-based assays were used to investigate the presence of neutralizing antibodies by inhibition of a cell-based functional activity.

In 130 patients treated with ELZONRIS 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 ELZONRIS.

- 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 ELZONRIS.

Anti-Product Antibody Effects on Pharmacokinetics
The presence of ADA had a clinically significant effect on the pharmacokinetics of tagraxofusp. Pharmacokinetic data obtained following doses given in Cycle 3 showed increased titers of anti-drug antibodies and reduced free ELZONRIS concentration in most plasma samples. Following administration of tagraxofusp 12 mcg/kg via 15-minute infusion in patients with pre-existing anti-drug antibodies, the mean (SD) volume of distribution of tagraxofusp is 21.2 (25.4) L, clearance is 13.9 (19.4) L/hr, AUC is 151 (89.2) hr·mcg/L and Cmax is 80.0 (82.2) mcg/L.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess the carcinogenic or genotoxic potential of tagraxofusp. Animal fertility studies have not been conducted with tagraxofusp.

13.2 Animal Toxicology and/or Pharmacology

At human equivalent doses greater than or equal to 1.6 times the recommended dose based on body surface area, severe kidney tubular degeneration/necrosis was observed in cynomolgus monkeys. At human equivalent doses equal to the recommended dose, degeneration/necrosis of the choroid plexus in the brain was observed in cynomolgus monkeys. The reversibility of this finding was not assessed at lower doses, but the finding was irreversible and became progressively more severe at a human equivalent dose 1.6 times the recommended dose, 3 weeks after dosing stopped.

14 CLINICAL STUDIES

14.1 First-Line Treatment of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

STML-401-0114 (NCT 02113982; Study 0114) was a multicenter, open-label, single-arm, clinical trial that included a prospective cohort of 13 patients with treatment-naive BPDCN. Treatment consisted of ELZONRIS 12 mcg/kg intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle. Patient baseline characteristics are presented in Table 5ble 5.

Table 5. Baseline Demographics of Patients with Treatment-Naive BPDCN

Parameter	N=13
Gender, N (%)	
Male	11 (84.6)
Female	2 (15.4)
Age (years), N (%)	
Median	65.0
Minimum, Maximum	22, 84
ECOG, N (%)	
0	8 (61.5)
1	5 (38.5)
BPDCN at Baseline, N (%)	
Skin	13 (100.0)
Bone Marrow	7 (53.8)
Peripheral Blood	3 (23.1)
Lymph Nodes	6 (46.2)
Viscera	2 (15.4)

The efficacy of ELZONRIS in patients with treatment-naive BPDCN was based on the rate of complete response or clinical complete response (CR/CRc). Key efficacy measures are presented in Table 6. The median time to CR/CRc was 57 days (range: 14 to 107).

Table 6. Efficacy Measures in Patients with Treatment-Naive BPDCN

Parameter	N=13
CR/CRc* Rate, N (%)	7 (53.8)
(95% CI)	(25.1, 80.8)
Duration of CR/CRc (months)	
Median	Not reached
Minimum, Maximum	3.9, 12.2
Duration of follow up (months)	
Median	11.5
Minimum, Maximum	0.2, 12.7

* CRc is defined as complete response with residual skin abnormality not indicative of active disease.

14.2 Relapsed or Refractory Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

STML-401-0114 (NCT02113982; Study 0114) was a multicenter, open-label, single-arm, clinical trial that included 15 patients with relapsed or refractory BPDCN. Treatment consisted of ELZONRIS 12 mcg/kg on days 1 to 5 of each 21-day cycle. Patient baseline characteristics are presented in Table 7.

Table 7. Baseline Demographics of Patients with Relapsed or Refractory BPDCN

Parameter	N=15
Gender, N (%)	
Male	13 (86.7)
Female	2 (13.3)
Age (years)	
Median	72
Minimum, Maximum	44, 80
ECOG, N (%)	
0	5 (33.3)
1	10 (66.7)
BPDCN at Baseline, N (%)	
Skin	13 (86.7)
Bone marrow	9 (60.0)
Lymph node	8 (53.3)
Visceral	4 (26.7)
Peripheral blood	1 (6.7)

In the 15 patients with relapsed/refractory BPDCN, one patient achieved CR (duration: 111 days) and one patient achieved a CRc (duration: 424 days).

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

ELZONRIS (tagraxofusp) concentrate for solution for infusion is a preservative-free, sterile, clear, colorless, 1 mg in 1 mL solution supplied in a single-dose glass vial. Each carton contains one vial.

15.2 Storage and Handling

Store and transport frozen (-20 °C ±5 °C). Protect ELZONRIS from light by storing in the original package until time of use. Allow vials to thaw at 25 °C or below for up to 1 hour in the outer carton. *[see Dosage and Administration (5.3)]*. Do not refreeze the vial once thawed. Do not use beyond expiration date on container.

16 SHELF LIFE

Unopened vial

The expiry date of the product is indicated on the packaging materials [*see Storage and Handling 15.2*].

After opening

From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately *[see Dosage and Administration 5.3]*.

After preparation of solution for infusion

Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

17 Manufacturer:
Stemline Therapeutics, Inc., NY, USA

18 Marketing Authorization Holder:
Stemline Israel Ltd., PO box 44, Tel-Mond, zip code 4065001

19 Registration Number:
172-66-36969-00

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