swissmedic

Date: 26 June 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ELZONRIS

International non-proprietary name: tagraxofusp
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 1mg / mL
Route(s) of administration: intravenous
Marketing authorisation holder: Stemline Therapeutics Switzerland GmbH
Marketing authorisation no.: 68797
Decision and decision date: approved on 3 February 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BLQ	Below the Limit of Quantification
BPDCN	Blastic plasmacytoid dendritic cell neoplasm
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CLS	Capillary leak syndrome
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CR	Complete response
CYP	Cytochrome P450
DBL	Data base lock
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
DT	Diphtheria toxin
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECLIA	Electrochemiluminescent immunoassay
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HSCT	Haematopoietic stem cell transplant
IC/EC_{50}	Half maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL	Interleukin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
MDS	Myelodysplastic syndrome
N/A	Not applicable

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

NCCN	National Comprehensive Cancer Network
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
R/R	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplantation
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for tagraxofusp in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 17 September 2020.

2.2 Indication and dosage

2.2.1 Requested indication

ELZONRIS is indicated for the treatment of adult patients and in paediatric patients 2 years and older with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

2.2.2 Approved indication

ELZONRIS is indicated for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The proposed dosage is 12 µg / kg tagraxofusp, administered once daily as intravenous infusion over 15 minutes 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. The treatment should be continued until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	19 April 2022
Formal control completed	20 April 2022
List of Questions (LoQ)	20 June 2022
Response to LoQ	26 September 2022
Preliminary decision	15 November 2022
Response to preliminary decision	12 January 2023
Final decision	3 February 2023
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical context

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare, clinically aggressive haematologic malignancy. BPDCN arises from the proliferation of malignant plasmacytoid dendritic cells and most commonly manifests as cutaneous lesions with or without bone marrow involvement and leukaemic dissemination. The tumour cells express the cell surface antigens CD4, CD56 and CD123 (= α-chain of the interleukin 3 receptor).

The precise incidence of BPDCN is difficult to estimate due to constantly changing nomenclature. BPDCN accounts for 0.44% of all haematologic malignancies. It can occur across all age groups but is most commonly diagnosed in adults, with a predominance in male patients. There is no standardised approach for first-line or relapsed/refractory (R/R) disease and there is no therapy specifically approved for BPDCN in Switzerland. According to international treatment guidelines (NCCN, Onkopedia), treatment commonly includes intensive chemotherapy regimens or tagraxofusp, where available. Apart from data for tagraxofusp, only retrospective data on outcome are available in the literature.
Median overall survival (OS) is approximately 8 months when patients are treated with chemotherapy only (Pagano et al, 2013[1], Garnache-Ottou F. et al. 2019[2]). With haematopoietic stem cell transplant (HSCT) after induction treatment, OS is remarkably prolonged up to a median of 49 months (Garnache-Ottou F et al., 2019). The disease has a high propensity to relapse. Treatment options for R/R disease are only poorly defined and the choice of treatment is influenced by prior therapy.

Tagraxofusp is a cytotoxin that is composed of diphtheria toxin linked to recombinant human interleukin 3 (IL-3). The IL-3 binds to IL-3 receptors that are present on BPDCN cells. Tagraxofusp is then internalised by the BPDCN cells and the diphtheria toxin leads to cell death.

[1] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica. 2013; 98 (2):239-246. doi:10.3324/haematol.2012.072645
[2] Garnache-Ottou F. et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? *Blood Adv* 2019; 3 (24): 4238–4251.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality aspects

4.1 Drug substance

Tagraxofusp is a 524 amino acid-long diphtheria toxin (DT)-interleukin-3 (IL-3) fusion protein. A truncated version of DT is engineered without its carboxy-terminal receptor-binding domain, which is replaced with the entire sequence of human IL-3.
The molecular weight of tagraxofusp is approximately 57,690 daltons.

Tagraxofusp is expressed in *Escherichia coli*. A two-tiered cell banking system of master cell bank and working cell bank (WCB) is in place. The manufacturing process consists of three main steps: microbial fermentation, harvest and recovery of inclusion bodies (IBs), and purification. After thawing of the WCB vial and a period of microbial growth, fermentation in batch mode is performed in a bioreactor. The cells are harvested by centrifugation and lysed by homogenisation. The IBs are collected by centrifugation, washed and stored frozen. The protein is refolded and is purified by chromatography and ultrafiltration/diafiltration steps.

The manufacturing processes for tagraxofusp drug substance are validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for tagraxofusp drug substance, including changes to production scale. However, comparability studies – which included batch release data, extended characterisation data and stress stability data – demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the tagraxofusp drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the tagraxofusp drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity and potency (cytotoxicity bioassay and receptor binding assay). Specifications are based on clinical experience, batch analysis data and stability data, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for several batches of tagraxofusp drug substance, including clinical and process validation batches, were provided. All specific analytical methods are described and are fully validated.

The tagraxofusp drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Tagraxofusp concentrate for solution for infusion 1 mg/vial (1 mg/mL) is a sterile, clear, colourless solution; a few white to translucent particles may be present. The finished product is presented in a 2 ml glass vial with rubber stopper and a flip-off seal.
The concentrate for solution for infusion is a buffered, isotonic, preservative-free solution, which is diluted with 0.9% sodium chloride solution to the target concentration prior to administration.

The excipients – trometamol, sodium chloride, sorbitol and water for injection – are of compendial grade and commonly used for the formulation of biopharmaceuticals.
Several drug product dosage strengths, formulations, presentations and filling facilities were used during clinical development. However, comparability studies – which included batch release data,

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

extended characterisation data and stress stability data – demonstrated comparability of the relevant quality attributes between the different processes.
The materials of the Type I glass vial and rubber stopper meet compendial requirements.
Compatibility studies were conducted to establish the in-use stability of the diluted drug product with the intended materials and conditions of use.

The drug product manufacturing process consists of thawing of the bulk drug substance, compounding of bulk solution, sterile filtration and aseptic filling, stoppering, sealing and visual inspection.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including clinical batches and process validation batches, were provided. All batch release data comply with the drug product specifications valid at the time of testing. All specific analytical methods are validated.

The vials are stored at -20°C ± 5°C protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product have been demonstrated.
Safety of the product with regard to non-viral contaminants is adequately addressed.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Non-clinical aspects

5.1 Pharmacology

Tagraxofusp bound to the human interleukin 3 receptor alpha subunit (IL-3RA) with a Kd of 470 nM, which is in the same range as the Kd of human IL-3 binding to IL-3RA (670 nM). As cynomolgus monkey and human IL-3 and CD123 have 85% and 92% amino acid sequence homology, binding to monkey CD123 was assumed but not investigated. The compound did not bind to mouse CD123.

Tagraxofusp exhibited anti-tumour activity against blastic plasmacytoid dendritic cell neoplasm (BPDCN) *in vitro*, with IC_{50} values in the femtomolar to picomolar range. *In vivo*, tagraxofusp treatment (2 µg/mouse, daily intraperitoneal injection for 5 consecutive days) significantly reduced the number of BPDCN cells in the peripheral blood, spleen and bone marrow, and prolonged the survival of immunodeficient mice implanted with acute myeloid leukaemia and BPDCN cells.

In tissue cross reactivity studies on frozen sections, investigators did not detect any reactivity with tagraxofusp in healthy human tissue, whereas reactivity was observed in cancerous cells expressing high levels of IL-3R. Thus, the likelihood of off-target pharmacology is low.

No dedicated safety pharmacology studies were conducted but these endpoints were incorporated into GLP-compliant repeat-dose, multiple-cycle toxicity studies of tagraxofusp in cynomolgus monkeys. There were no tagraxofusp-related effects on qualitative or quantitative ECG parameters. Histology examinations revealed moderate degeneration/necrosis of the choroid plexus of the brain at doses ≥ 30 µg/kg that increased during the recovery period. These effects were treatment-related and may be relevant for the clinical setting but can be monitored. No clinical evidence of increased pulmonary or CNS toxicity was observed in the treated patients. Choroid plexus lesions are listed as an important potential risk in the RMP and the information for healthcare professionals. The immunohistochemistry study noted in the RMP was provided at the request of Swissmedic and is accepted.

5.2 Pharmacokinetics

After intravenous (IV) administration for 5 consecutive days per cycle (treatment for 1 to 3 cycles), C_{max} and AUC increased dose-dependently after the first dose of each treatment cycle. No sex-related differences in exposure were observed. Monkeys exhibited an ADA response throughout the study. The development of ADAs increased with treatment duration and led to reduced exposure.
The volume of distribution was similar to the total blood volume in monkeys, suggesting that tagraxofusp did not extensively distribute outside the systemic blood circulation. The $t_{1/2}$ did not change remarkably between the cycles (approx. 0.5 h). In general, the toxicokinetic profiles for each dose were analogous to that for a single dose.

In line with ICH S6, the applicant did not generate data on distribution, metabolism or excretion. Due to highly selective binding affinity of tagraxofusp to human IL-3R, the risk of pharmacokinetic drug-drug interactions is considered low.

5.3 Toxicology

The applicant selected the cynomolgus monkey as the pharmacologically relevant species. Study designs and parameters were consistent with ICH S6 and ICH S9. The pivotal studies were in compliance with GLP regulations. The animals received tagraxofusp IV in 1 to 3 cycles of 5 consecutive daily doses, separated by 21 to 22-day periods without dosing. This is similar to the dosage regimen in patients.

In the 5-day studies, one male receiving 80 µg/kg and one female receiving 60 µg/kg were euthanised due to severe clinical signs including severe renal dysfunction, decreased activity, decreased motor skills, limbs cold to touch, no pain response, severe tubular degeneration and necrosis. In addition, one female receiving 60 µg/kg/day was euthanised on the first day of recovery due to renal toxicity. One female receiving 45 µg/kg in the 3-month GLP study was euthanised on Day 9. The cause of this

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

monkey's morbidity could not be identified. Tagraxofusp-related mortality is also reported in the literature in one female monkey receiving 100 µg/kg that died after 3 doses due to moderate to severe vasculitis in multiple tissues. In these animals, some of the following effects were observed: multifocal haemorrhage and perivascular oedema in the brain, fibrin deposition in the spleen, glomeruli and bone marrow, bone marrow necrosis and necrosis of venule walls in the lymph node. These findings suggest that tagraxofusp treatment damaged blood vessels or caused inappropriate effects on coagulation. Capillary leak syndrome is an important identified risk.

The main target organs of toxicity identified in the surviving animals were the choroid plexus, thymus, kidneys, liver and the blood compartment. In the 5-day studies, surviving monkeys receiving ≥30 µg/kg and recovery monkeys receiving 60 µg/kg showed study drug-related inflammation and necrosis/degeneration in the choroid plexus. Data submitted at the request of Swissmedic as well as clinical evidence suggest that this effect is monkey-specific and is unlikely to occur in humans. There were tagraxofusp-related reversible decreases in lymphocytes (up to -40%) at ≥ 30 µg/kg that correlated with lymphoid depletion in the thymus. Generalised lymphoid depletion of the thymus was present in all terminal, unscheduled death and recovery animals at 60 µg/kg and in terminal females at 30 µg/kg. Severe renal tubular degeneration and necrosis were detected that correlated with the increased kidney weight in terminal males at 60 µg/kg. At recovery, most renal effects were at least partially resolved. Renal failure and acute kidney injury in patients are mentioned in the information for healthcare professionals. Study drug-related adverse effects on liver enzymes were detected in all groups (≥ 40 µg/kg) post-first dose. Microscopically, hepatocellular necrosis and vacuolation correlated with the increased liver weight in terminal males at 60 µg/kg. Acute hepatic insufficiency and hepatic encephalopathy have been reported in patients receiving high doses of tagraxofusp and are mentioned in the information for healthcare professionals. The assessment of local tolerance showed procedure-dependent haemorrhage and inflammation at the injection site.

Considering that 60 µg/kg corresponds to a human equivalent dose which is ≥1.6-fold the recommended dose based on body surface area, there are no safety margins. This can be accepted considering the indication. Aside from the effects on the thymus and choroid plexus, the animals completely or partially recovered during the 3-week period following the 5-day tagraxofusp administration. Toxicities seemed less pronounced in the 3-month study, which is probably related to the time-dependent appearance of ADAs and associated decrease in exposure in monkeys.

No genotoxicity, carcinogenicity or reproductive and developmental toxicity studies were conducted according to ICH S6 and ICH S9 regulations.

No juvenile animal studies were conducted. The European regulators granted a waiver for tagraxofusp in the treatment of BPDCN in all subsets of the paediatric population.

The risk for the environment is considered to be negligible.

The non-clinical safety specifications in the RMP adequately address the non-clinical findings and their relevance for clinical use.

5.4 Non-clinical conclusions

The submitted documentation is considered appropriate to conduct a risk assessment for tagraxofusp. The submitted nonclinical data are in line with ICH S9 and ICH S6 guidelines and support the approval of tagraxofusp in the proposed indication. The relevant information has been included in the information for healthcare professionals.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

In order to interpret the available tagraxofusp PK data, some insight into the bioanalytical method used to measure tagraxofusp plasma concentrations is required.

Tagraxofusp is a recombinant fusion protein composed of interleukin 3 (IL-3) and truncated diphtheria toxin (DT). Tagraxofusp plasma concentrations were measured with a conventional dual antibody sandwich immunoassay employing electrochemiluminescence (ECL) detection (ECLIA). The capture antibody on the plate was a rat anti-hIL-3 antibody, while the antibody carrying the sulfo-TAG emitting the ECL signal for concentration measurements binds to the DT domain of tagraxofusp. Circulating DT antibodies interfere with the measurement of the tagraxofusp plasma concentrations. Expressed in different terms, the assay measures the “free” tagraxofusp plasma concentrations (=> not tagraxofusp /DT ADA complexes) only.

ADME

Biopharmaceutical development

Tagraxofusp is administered as an intravenous infusion. A total of three different formulations were administered in clinical studies. Two of them were frozen liquid formulations; the third was a lyophilised formulation. The liquid formulation containing 1.0 mg/mL tagraxofusp was administered in the pivotal study STML-401-0114 to the majority of the patients, and is identical to the proposed commercial formulation. Seven AML patients in Study STML-401-0114 received the lyophilised formulation. Because of the small number of patients receiving the lyophilised formulation and the high variability of the data, it was not possible to draw any conclusions regarding the relative bioavailability of the two formulations.

Dose proportionality

As there were not enough patients without pre-existing DT ADAs across dose levels, a formal statistical evaluation of dose proportionality based on non-compartmental methods was not feasible. However, it was possible to fit the tagraxofusp plasma concentrations across a dose range of 7 to 16 µg/kg with a fully linear PopPK model. Therefore, major deviations from dose proportionality appear to be unlikely.

Pharmacokinetics after multiple dosing

“Free” tagraxofusp exposures decreased with increasing DT ADA titers. Apparently, tagraxofusp boosted the pre-existing DT ADAs by its DT domain during treatment. On Day 5 of the first treatment cycle in Study STML-401-0114, the tagraxofusp exposures were higher than on Day 1 of Cycle 1, but in Cycle 3, the “free” tagraxofusp plasma concentrations were barely measurable.

Distribution

The mean tagraxofusp volume of distribution in BPDCN patients without DT ADAs (n=4) on C1D1 was 5.11 L. For patients with pre-existing DT ADAs (n=25) it was 21.2 L.

Metabolism & elimination

No *in vitro* or clinical metabolism studies were conducted for tagraxofusp. This is acceptable considering the biological nature of the molecule.

The mean tagraxofusp clearance and half-life in BPDCN patients without DT ADAs (n=4) on C1D1 were 7.16 L/h and 0.714 h, respectively. The corresponding values for patients with pre-existing DT ADAs (n=25) were 13.9 L/h and 1.18 h, respectively.

The incidence of ADAs directed against the IL-3 domain of tagraxofusp was considerably lower compared to the DT ADAs. Their effect on tagraxofusp exposures appeared to be small compared to the effect of the DT ADAs.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Special populations / intrinsic factors

No dedicated studies in special populations were conducted with tagraxofusp. Investigation of the impact of selected covariates including age, body weight, sex, race, cancer type, and hepatic and renal function in a PopPK analysis was attempted. However, after including ADAs as a covariate in the model, none of the others reached statistical significance

The overall dataset contained 127 patients, including 47 (37%) BPDCN patients. The majority of the patients had normal hepatic function according to NCI-ODWG critieria. There was a sufficient number of patients with mild hepatic impairment, two patients with moderate hepatic impairment and no patients with severe hepatic impairment. The majority of the patients (47%) had mild renal impairment, 33% had normal renal function, 20% had moderate renal impairment and none had severe renal impairment. The overall age range of the patients in the dataset was 21 to 87 years. The body weight range was 46.7 to 162 kg. The age and weight range of the BPDCN patients was 22 to 84 years and 61.5 to 128 kg. It should be noted that the dataset did not include any paediatric patients.

The final model describing the PK of free tagraxofusp was a one-compartment model with linear elimination. The model also included the estimation of the fraction of dose escaping immediate ADA binding in plasma (F1). For technical reasons it was necessary to model the C1D1, C1D3-5 and C3-4 data separately. The C1D3-5 model was the reference model because it was assumed that the impact of pre-existing ADAs would be attenuated by then and the impact of treatment-emergent ADAs would not yet be fully developed.

Considering correlations between covariates, only body weight, eGFR and hepatic impairment (the two patients with moderate hepatic impairment were added to the mild hepatic impairment group) were tested. After accounting for the impact of ADAs on tagraxofusp PK, none of these covariates improved the fit in the reference C1D3-5 model. The estimated fraction of dose escaping immediate ADA binding in plasma (F1) decreased with increasing ADA titers.

The relative standard error of most parameter estimates, including the factors describing the impact of ADAs on tagraxofusp exposures, was high in all three models, indicating a low precision of the estimates.

At the early measurement time points, the model described the data reasonably well. The main issues were an under-estimation of the variability of the data at later measurement time points and the over-estimation of the fraction of BLQ concentrations. Therefore, the model was not suitable for simulations.

Interactions

No *in vitro* or clinical interaction studies were conducted for tagraxofusp. This is acceptable considering the biological nature of the molecule and its mechanism of action.

6.2 Dose finding and dose recommendation

The investigator-initiated study 50047 – a single-arm, open-label phase 1/2 first in human clinical study of tagraxofusp – served as dose finding study for the company-initiated pivotal Study 0114.

In total, 91 patients with acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), myelodysplastic syndrome (MDS) and BPDCN (first-line and relapsed/refractory (R/R)) were enrolled, and tagraxofusp was evaluated in 2 different regimens.

Based on the totality of data, a dose of 12.5 µg/kg/day for 5 days was considered to have the most favourable risk-benefit profile.

Based on the results of Study 50047, a standard 3+3 design with escalating doses of 7, 9, 12 or 16 µg/kg/day was administered in stage 1 of the pivotal study STML-401-0114 (Study 0114). Consistent with Study 50047, dose-limiting toxicity (DLT) identified in stage 1 of Study 0114 included capillary leak syndrome (CLS) and infusion-related reaction. The dose of 12 µg/kg/day was identified as the maximum tolerated dose (MTD) and considered to be the recommended phase 2 dose for the subsequent stages of Study 0114 (stage 2-4).

6.3 Efficacy

The pivotal, non-randomised, open-label study STML-401-0114 (Study 0114) was submitted in support of the proposed indication. Study 0114 was a multi-centre phase 1/2 study of tagraxofusp in patients with BPDCN aged ≥ 18 years, initiated in 2014, conducted in the US and was divided into multiple stages including a pivotal confirmatory phase (= stage 3). Diagnosis of BPDCN was confirmed by a central pathology review. Patients were administered tagraxofusp by intravenous infusion over 15 minutes for 5 consecutive days of a 21-day cycle. All patients received anti-allergic premedication. Treatment continued until disease progression or another reason for withdrawal.

Stages 1 and 2 provided the basis for the design of stage 3. Stage 3 served as the pivotal confirmatory evidence for efficacy of tagraxofusp in patients with first-line BPDCN with complete response (CR) as a primary endpoint, comprising complete resolution of disease (CR) and complete resolution with minimal residual skin abnormality (CRc). Statistical significance was to be determined if the lower bound of the 95% confidence interval (CI) for CR was above 10%. Subsequent BPDCN patients were enrolled in stage 4, which was initiated to allow patients continued access to tagraxofusp in a clinical study setting to further characterise efficacy and safety of tagraxofusp and to evaluate a lyophilised formulation of tagraxofusp in a subset of patients. Patients treated in stage 1-3 received the proposed commercial liquid formulation.

Formal hypothesis testing of secondary endpoints was not planned; therefore, the analyses of all secondary endpoints were descriptive. Key secondary endpoints included objective response rate (ORR), bone marrow CR, proportion of patients who receive a stem cell transplant (SCT), overall survival (OS) and progression-free survival (PFS).

Final results were presented with a data base lock (DBL) of 13 March 2020. No further follow-up data were available. Overall, n=65 first-line BPDCN patients received the requested dose of tagraxofusp of 12 µg/kg/day. For details, see the“Properties / Effects” section of the attached information for healthcare professionals. At the DBL, 41/65 patients had died and 24 were censored.

The CR rate in the n=13 stage 3 patients was 53.8% (95% CI 25.1, 80.8), thereby meeting the prespecified criteria of statistical significance. The CR rate of the overall population (n=65) was 56.9% (95% CI 44.0, 69.2).

Median duration of CR was not reached for the stage 3 patients and was 24.9 months (95% CI 3.8, NE) for the overall population. A clinically relevant proportion of patients proceeded to an SCT (46% in stage 3; 32% overall). For further details on efficacy, please refer to the attached information for healthcare professionals.

Supportive efficacy data were provided by the European early access programme (EAP), with n=22 BPDCN patients evaluable at that time. CR rate was 66.7% in n=15 first-line patients.

6.4 Safety

Pooled safety analysis included data from 232 patients treated with tagraxofusp monotherapy, including 7 AML patients who received tagraxofusp at a dose of 16 µg/kg/day. Two-hundred-and-four patients received the requested dose of 12 µg/kg/day.
The median duration of exposure was 54.5 days (range 1, 1622); the median number of cycles started was 3 (range 1, 76).

Treatment-emergent adverse events (TEAEs) were observed in almost all patients exposed to tagraxofusp monotherapy (98.7%), with the following TEAEs being observed most frequently (≥ 30%): ALT increased (49.1%), hypoalbuminaemia (48.3%), AST increased (46.1%), nausea (43.5%), fatigue (43.1%), pyrexia (39.2%), peripheral oedema (36.2%) and thrombocytopenia (33.6%).

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Grade ≥ 3 TEAEs were present in 85.8% of patients, with the following TEAEs being observed most frequently (≥10%): thrombocytopenia (26.3%), AST increased (20.7%), ALT increased (20.3%), anaemia (19.8%) and febrile neutropenia (10.3%).

Serious adverse events (SAEs) were observed in 55.2% of patients, with CLS being the most common SAE with an incidence of 12.1%. The following SAEs occurred with an incidence of ≥ 3%: pyrexia (5.2%), febrile neutropenia (4.7%), pneumonia (3.0%) and sepsis (3.0%).

In total, 13.4% of patients experienced a grade 5 TEAE. The following grade 5 TEAEs were reported for more than 1 patient: CLS (2%), myocardial infarction, disease progression, lung infection, acute kidney injury, intracranial haemorrhage (1% each), cerebrovascular accident, pneumonia and acute respiratory failure (<1% each). The CLS cases (3 in BPDCN patients and 1 in an AML patient) were assessed by the Investigator as being tagraxofusp-related. There is a significant risk of CLS mortality associated with treatment with tagraxofusp. Therefore, a boxed warning for CLS is included in the information for healthcare professionals and risk mitigation strategies are implemented (please refer to the attached information for healthcare professionals).

TEAEs leading to dose discontinuation were observed in 13.4% and TEAEs leading to dose interruption in 55.6% of patients. Dose reductions were observed in 4% of the patients.

The rate of CLS was high in the European early access programme (54.2%), but the majority of events were grade ≤ 2 and no grade 5 CLS events were observed.

6.5 Final clinical and clinical pharmacology benefit-risk assessment

BPDCN is a very rare disease with a highly aggressive clinical course and a dismal prognosis. Treatment usually includes intensive chemotherapy regimens or tagraxofusp, where available. However, there is no standardised treatment approach and no approved therapy specifically for BPDCN available in Switzerland. The disease has a high propensity to relapse. Patients who received an HSCT in first complete remission have a higher median overall survival (OS) than patients treated with chemotherapy alone. Based on retrospective data, median OS is approximately 8 months when patients are treated with chemotherapy only and is prolonged up to a median of 49 months in patients receiving HSCT after induction treatment.

To support the requested indication, the applicant provided data from the pivotal phase 1/2 Study 0114 and supportive information from the European early access programme (EAP).

The pivotal Study 0114 met its primary endpoint in the confirmatory stage 3 population, treated in first line. In addition, a relevant proportion of patients were successfully bridged to stem cell transplant, which has the potential to cure. Initial efficacy results of the EAP are in line with the results of Study 0114. Even though uncertainties remain, mainly due to the early phase single-arm design, the small sample size and the limited hypothesis testing, the efficacy of tagraxofusp is considered sufficiently established and of clinical relevance.

The safety profile of tagraxofusp is non-trivial, including hepatotoxicity and potentially lethal capillary leak syndrome. However, the overall treatment-associated mortality is similar to what has been reported with empirical chemotherapy, and the haematological toxicity of tagraxofusp is lower. The relevant safety issues are reflected in the information for health care professionals (see attached).

Conclusion
In light of the rarity of the disease and the unmet medical need, the benefits outweigh the risks and the overall benefit-risk ratio is positive. As a condition, the applicant is requested to provide the results of a planned EU registry study.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for ELZONRIS was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Important Warning: Patients receiving ELZONRIS may experience **capillary leak syndrome** (CLS), which can be **life-threatening or fatal** if not adequately treated.

For more information, please refer to the chapters "Dosage/Administration", and "Warnings and precautions".

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ELZONRIS®

Composition

Active substance

Tagraxofusp.

Tagraxofusp is a diphtheria toxin-interleukin-3 (IL-3) fusion protein produced by recombinant DNA technology in *Escherichia coli*.

Excipients

Each vial contains trometamol, 1.98 mg sodium chloride, 50 mg sorbitol (E420), water for injections.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.

Each vial with 1 mL of concentrate for solution for infusion contains 1 mg tagraxofusp (1mg/ml, i.v.).

Clear, colourless liquid. A few white to translucent particles may be present.

Indications/Uses

ELZONRIS is indicated for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Dosage/Administration

ELZONRIS should be administered under the supervision of a physician experienced in the use of anti-cancer agents. Appropriate resuscitation equipment should be available.

The recommended dose is 12 µg tagraxofusp / kg body weight administered as an intravenous infusion over 15 minutes, once daily, on days 1-5 of a 21-day cycle. The dosing period may be

extended for dose delays up to day 10 of the cycle. Treatment should be continued until disease progression or unacceptable toxicity.

First treatment cycle

The first cycle of ELZONRIS should be administered in the in-patient setting. Patients should be monitored for signs and symptoms of hypersensitivity or capillary leak syndrome (CLS) until at least 24 hours after the last infusion.

Subsequent treatment cycles

ELZONRIS can be administered in the in-patient setting or in a suitable out-patient ambulatory care setting that is equipped for intensive monitoring of patients with haematopoietic malignancies undergoing treatment.

Pre-medication

Patients must be pre-medicated with a H_1-histamine antagonist (e.g. diphenhydramine hydrochloride), a H_2-histamine antagonist, a corticosteroid (e.g. 50 mg intravenous methylprednisolone or equivalent) and paracetamol approximately 60 minutes prior to the start of infusion.

Dose adjustment/titration

Vital signs should be monitored, and albumin, transaminases, and creatinine checked prior to preparing each dose of ELZONRIS. See Table 1 for recommended dose modifications and Table 2 for CLS management guidelines.

Vital signs should be monitored frequently during dosing.

Table 1: Recommended ELZONRIS dosing regimen modifications

Parameter	Severity criteria	Dose 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 pre-treatment weight on prior treatment day	See CLS Management Guidelines (Table 2)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold treatment until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 µmol/L) or creatinine clearance < 60 mL/minute	Withhold treatment until serum creatinine resolves to ≤ 1.8 mg/dL (159 µmol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold treatment until systolic blood pressure is < 160 mmHg or > 80 mmHg.

Parameter	Severity criteria	Dose modification
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold treatment until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38 °C	Withhold treatment until body temperature is < 38 °C.
Hypersensitivity reactions	Mild or moderate	Withhold treatment until resolution of any mild or moderate hypersensitivity reaction. Resume ELZONRIS at the same infusion rate.
	Severe	ELZONRIS must be permanently discontinued.

Table 2: Capillary leak syndrome (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	
During ELZONRIS dosing	Serum albumin < 3.5 g/dL	Administer 25 g intravenous albumin every 12 hours (or more frequently if practical) until serum albumin is ≥ 3.5 g/dL AND not reduced by ≥ 0.5 g/dL from the value measured prior to dosing initiation of the current cycle.	Withhold dosing until the relevant CLS sign/symptom has resolved [1]
	Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle		
	A pre-dose body weight that is increased by ≥ 1.5 kg over the previous day's pre-dose weight	Administer 25 g intravenous albumin (every 12 hours or more frequently as practical), and manage fluid status if 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 pre-dose weight).	
	Oedema, fluid overload and/or hypotension	Administer 25 g intravenous albumin (every 12 hours, 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 withheld:
- ELZONRIS administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat haemodynamic instability.
- Administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat haemodynamic instability (e.g., required administration of intravenous fluids and/or vasopressors to treat hypotension, even if resolved).
- Administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is haemodynamically stable.

Special dosage instructions

Patients with hepatic disorders

No data are available for patients with hepatic impairment (see “Pharmacokinetics"). Patients with severe hepatic impairment were not studied in the clinical trial.

Patients with renal disorders

No data are available for patients with renal impairment (see "Pharmacokinetics"). Patients with severe renal impairment were not studied in the clinical trial.

Elderly patients

No dose adjustment is required for patients over 65 years of age. Generally, safety was similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with ELZONRIS.

Children and adolescents

ELZONRIS is not approved for use in the paediatric population. No dosage recommendation can be given. Currently available data are described under the headings "Undesirable Effects" and "Clinical Efficacy".

Mode of administration

ELZONRIS is for intravenous use.

The prepared dose of diluted ELZONRIS should be administered via an infusion syringe pump over 15 minutes. The total infusion time should be controlled using an infusion syringe pump to deliver the entire dose and the sodium chloride 9 mg/mL (0.9%) solution for injection within 15 minutes.

ELZONRIS must not be administered as an intravenous push or bolus. It should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products (see section “Other information, Incompatibilities”).

Prior to infusion, venous access should be established and maintained with sodium chloride 9 mg/mL (0.9%) solution for injection.

For instructions on preparation and administration of the medicinal product, see section ““Other information, Instructions for handling”.

Contraindications

ELZONRIS is contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Capillary leak syndrome

Capillary leak syndrome (CLS), including life-threatening and fatal cases, has been reported with most events occurring during the first five days of the first cycle of treatment. The most frequent signs and symptoms of CLS included weight gain, hypoalbuminaemia, and hypotension. The incidence of weight gain, hypoalbuminaemia, hypotension, and blood alkaline phosphatase increased are each higher among patients who experienced CLS compared to patients that did not experience CLS. Renal failure and acute kidney injury have been reported in two patients with BPDCN and in one patient with AML secondary to CLS (see section “Undesirable effects”).

Before initiating therapy, ensure that the patient has adequate cardiac function and serum albumin ≥ 3.2 g/dL. During treatment, regularly monitor serum albumin levels prior to the each dose, or more often as clinically indicated. Additionally, assess patients for other signs/symptoms of CLS including weight gain, new onset or worsening oedema, including pulmonary oedema, and hypotension including haemodynamic instability (see Table 2).

Patients must be urged to watch for CLS symptoms and instructed as to when to seek immediate medical attention. Intravenous albumin supplementation and dosing interruptions may be required (see section “Dosage/Administration”).

Hypersensitivity reactions

Severe hypersensitivity reactions have been reported with ELZONRIS. Commonly reported reactions include rash (generalised / maculo-papular); wheezing; pruritus; angioedema; swelling in the face; and flushing (see section “Undesirable effects”). Monitor patients for hypersensitivity reactions during

treatment. The infusion with ELZONRIS must be interrupted if hypersensitivity reactions occur and appropriate measures must be initiated (see section “Dosage/Administration”).

Haematological abnormalities

Thrombocytopenia and neutropenia have been reported in patients treated with ELZONRIS monotherapy (see section “Undesirable effects”). The majority of events were reported in cycle 1 and cycle 2 of treatment. They were not dose-limiting and did not recur in subsequent cycles. Patients should be routinely monitored and treated as clinically indicated.

Tumour lysis syndrome

ELZONRIS can cause tumour lysis syndrome (TLS), which may be fatal as a result of its rapid anti-tumour activity (see section “Undesirable effects”).

TLS must be identified 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.

Hepatotoxicity

Treatment with ELZONRIS has been associated with elevations in liver enzymes (see section “Undesirable effects”). Acute hepatic failure and liver encephalopathy has been reported in a patient treated with ELZONRIS at a higher dose (16 µg/kg). During treatment, regularly monitor ALT and AST levels prior to each dose. Temporarily withhold treatment if transaminases rise to greater than 5 times the upper limit of normal and resume treatment when transaminase elevations are ≤ 2.5 times the upper limit of normal (see section “Dosage/Administration”).

Choroid plexus lesions

Choroid plexus inflammation was identified during non-clinical studies (see section “Preclinical data”). While not observed in clinical studies, if clinical symptoms or signs suggestive of central nervous system (CNS) damage occur, full clinical and neurodiagnostic imaging examination, including fundoscopy and brain magnetic resonance imaging, is recommended.

BPDCN with CNS involvement

It is not known whether tagraxofusp crosses the blood brain barrier. Other treatment alternatives should be considered if CNS disease is present.

Women of childbearing potential/contraception

In women of childbearing potential, a negative pregnancy test should be obtained within 7 days prior to initiation of therapy. Effective contraception should be used before the first dose is administered and for at least one week after the last dose.

Hereditary fructose intolerance

Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

A detailed history with regard to HFI symptoms has to be taken from each patient prior to being given this medicinal product.

Sodium sensitivity

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

Interactions

No interaction studies have been performed.

Pregnancy, lactation

Women of childbearing age
In women of childbearing potential, a negative pregnancy test should be obtained within 7 days prior to initiation of therapy. Effective contraception should be used before the first dose is administered and for at least one week after the last dose.

Pregnancy

There are no data from the use of ELZONRIS in pregnant women.

Animal reproduction studies have not been conducted with tagraxofusp (see section “Preclinical data”).

ELZONRIS should not be used during pregnancy unless the clinical condition of the woman requires treatment with tagraxofusp.

Lactation

It is unknown whether tagraxofusp/metabolites are excreted in human milk.

A risk to breast-feeding newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with ELZONRIS and for at least one week after the last dose.

Fertility

No fertility studies have been conducted with tagraxofusp (see section “Preclinical data”). There are no data on the effect of tagraxofusp on human fertility.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most serious adverse reaction that may occur during ELZONRIS treatment is CLS (see sections “Dosage/Administration” and “Warnings and precautions”) which was reported in 18% of patients, with a median time to onset of CLS of 6 days.

Adverse reactions occurring in ≥ 20% of patients treated with ELZONRIS were increased transaminases, hypoalbuminaemia, thrombocytopenia, nausea, pyrexia, fatigue and peripheral oedema.

Adverse reactions grade 3 and above according to the Common Terminology Criteria for Adverse Events (CTCAE) and occurring in > 5% of patients were increased transaminases, thrombocytopenia, anaemia, capillary leak syndrome and neutropenia.

List of adverse reactions

The adverse reaction frequency is listed by MedDRA System Organ Class (SOC) preferred terms. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10) and uncommon (≥ 1/1000, < 1/100).

The adverse reactions described in this section were identified in clinical studies of patients with haematologic malignancies (N=225), including 89 patients with BPDCN. In these studies, ELZONRIS was administered as monotherapy at doses of 7 µg/kg (12/225, 5%), 9 µg/kg (9/225, 4%) and 12 µg/kg (204/225, 91%). Incidence and severity of adverse reactions in patients with BPDCN were similar to those of the population studied overall.

Table 3: Tabulated list of adverse reactions by MedDRA System Organ Class

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
Infections and infestations		
Uncommon	Pneumonia Urinary tract infection Cellulitis Bacterial test positive	Bacterial test positive
Blood and lymphatic system disorders		
Very Common	Thrombocytopenia (27.1%) [a] Anaemia (14.7%)	Thrombocytopenia (21.3%)
Common	Neutropenia Leukopenia Lymphopenia Febrile neutropenia Leukocytosis	Anaemia Neutropenia Leukopenia Lymphopenia Febrile neutropenia
Uncommon	None	Leukocytosis
Immune system disorders		
Common	Cytokine release syndrome	Cytokine release syndrome
Metabolism and nutrition disorders		
Very Common	Weight increased (17.8%) Hypoalbuminaemia (39.6%)	None
Common	Tumour lysis syndrome Hypokalaemia Hyperglycaemia Hyponatraemia Hyperuricaemia Hypomagnesaemia Hypocalcaemia Hypophosphataemia Hyperkalaemia Hyperphosphataemia Blood creatine phosphokinase increased International normalised ratio (INR) increased Blood lactate dehydrogenase increased Decreased appetite	Tumour lysis syndrome Hyperglycaemia Hypoalbuminaemia
Uncommon	Acidosis Lactic acidosis Blood creatinine phosphokinase decreased Blood urea increased	Hypokalaemia Hyponatraemia Hyperuricaemia Hypocalcaemia Hypophosphataemia

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
	Protein total decreased	Acidosis Lactic acidosis Blood lactate dehydrogenase increased
Psychiatric disorders		
Common	Confusional state	None
Uncommon	Insomnia Anxiety Depression Mental status changes	None
Nervous system disorders		
Common	Syncope [b] Dizziness Headache	Syncope
Uncommon	Cerebrovascular accident Encephalopathy [c] Memory impairment Disturbance in attention Amnesia Somnolence Facial paralysis Paraesthesia Peripheral motor neuropathy Peripheral sensory neuropathy Parosmia Dysgeusia	Cerebrovascular accident Encephalopathy
Eye Disorders		
Common	Vision blurred [d]	None
Uncommon	Conjunctival haemorrhage Ocular hyperaemia Vitreous floaters	None
Blood and lymphatic system disorders		
Uncommon	Activated partial thromboplastin time prolonged	None
Cardiac Disorders		
Common	Tachycardia Sinus tachycardia	None

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
Uncommon	Pericardial effusion Atrial fibrillation Myocardial infarction Supraventricular extrasystoles Ventricular fibrillation Bradycardia Electrocardiogram QT prolonged	Sinus tachycardia Pericardial effusion Myocardial infarction Ventricular fibrillation Electrocardiogram QT prolonged
Vascular disorders		
Very Common	Capillary leak syndrome (17.8%) Hypotension (15.6%) [e]	None
Common	Flushing [f]	Capillary leak syndrome Hypotension
Uncommon	Hypertension Haematoma	Hypertension
Respiratory, thoracic and mediastinal disorders		
Common	Pulmonary oedema Pleural effusion Dyspnoea [g] Hypoxia	Pulmonary oedema
Uncommon	Atelectasis Bronchiestasis Cough Oropharyngeal pain Pneumonitis Respiratory failure Tachypnoea Wheezing Epistaxis	Respiratory failure Dyspnoea Hypoxia
Gastrointestinal Disorders		
Very Common	Nausea (23.6%) [h] Vomiting (12.9%)	None
Common	Diarrhoea Constipation Dyspepsia Dry mouth Stomatitis	None
Uncommon	Pancreatitis Abdominal pain Dysphagia Abdominal distension Gingival bleeding	Pancreatitis Nausea

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
	Tongue haematoma	
Hepatobiliary disorders		
Very Common	Transaminases increased (45.8%) [i]	Transaminases increased (24.4%)
Common	Hyperbilirubinemia [j] Blood alkaline phosphatase increased	None
Uncommon	Blood fibrinogen decreased	None
Skin and subcutaneous tissue disorders		
Common	Rash [k] Pruritus Hyperhidrosis	None
Uncommon	Petechiae Alopecia Angioedema Erythema nodosum Palmar-plantar erythrodysesthesia syndrome Stasis dermatitis Swelling of the face Urticaria	Angioedema Rash
Musculoskeletal and connective tissue disorders		
Common	Back pain Arthralgia Myalgia Bone pain [l] Pain in extremity	None
Uncommon	Rhabdomyolysis Muscular weakness Muscle spasms Musculoskeletal pain	Rhabdomyolysis Arthralgia Back pain
Renal and urinary disorders		
Common	Acute kidney injury Blood creatinine increased	None

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
Uncommon	Renal failure Dysuria Pollakiuria Proteinuria Urinary retention Urinary tract pain	Acute kidney injury
Reproductive system and breast disorders		
Uncommon	Breast pain Oedema genital	None
General disorders and administration site conditions		
Very Common	Pyrexia (23.1%) Oedema peripheral (19.6%) [m] Fatigue (19.1%) [n] Chills (16.9%)	None
Common	Pain Influenza-like illness Chest pain	Fatigue
Uncommon	Malaise Drug intolerance Hypothermia Non-cardiac chest pain Systemic inflammatory response syndrome	Pyrexia Oedema peripheral Chills Drug intolerance
Injury, poisoning and procedural complications		
Common	Infusion-related reaction Contusion	None
Uncommon	None	Infusion-related reaction

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes syncope and presyncope.
[c] Includes encephalopathy and metabolic encephalopathy.
[d] Includes vision blurred and visual impairment.
[e] Includes hypotension, procedural hypotension and orthostatic hypotension.
[f] Includes flushing and hot flush.
[g] Includes dyspnoea and exertional dyspnoea.
[h] Includes nausea and retching.
[i] Includes transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, hepatic enzymes increased.
[j] Includes hyperbilirubinaemia and blood bilirubin increased.
[k] Includes rash, rash pustular, rash maculo-papular, rash erythematous, rash generalised, rash macular
[l] Includes bone pain and coccydynia.
[m] Includes oedema peripheral, generalised oedema, oedema, peripheral swelling, fluid retention, fluid overload, periorbital oedema, hypervolaemia.

[n] Includes fatigue, asthenia, lethargy.

Description of specific adverse reactions and additional information

Capillary leak syndrome

Capillary leak syndrome was reported in 18% (40/225), with 11% (24/225) Grade 2, 4% (10/225) Grade 3, 1% (3/225) Grade 4, and fatal in 1.3% (3/225). Of the patients that resumed treatment after experiencing an event of CLS, only 1 patient experienced a recurrence of CLS. The median time to onset of CLS was short (6 days), with all but 3 patients experiencing the first onset of CLS in cycle 1. No patient experienced the first onset of CLS after cycle 2. The overall incidence of CLS was similar in patients with BPDCN (21%, 19/89), including 14% (12/89) Grade 2, 2% Grade 3 (2/89), 2% Grade 4 (2/89) and 3 fatal cases (3%). Patients are required to have adequate cardiac function prior to administration of ELZONRIS (see sections “Dosage/Administration” and “Warnings and precautions”).

Hepatotoxicity

ALT and AST elevations were reported as adverse reactions in 40% (90/225) and 39% (87/225) of patients treated with ELZONRIS monotherapy, respectively. ≥ Grade 3 ALT and AST increased were reported in 18% (40/225) and 19% (42/225) of patients, respectively. Elevated liver enzymes occurred in the majority of patients in cycle 1 and were reversible following dose interruptions (see section “Warnings and precautions”). Similar onset time and incidence were observed in patients with BPDCN, with 51% (45/89) of patients experiencing adverse events of ALT and AST elevations, with ≥ Grade 3 ALT and AST increased reported in 28% (25/89) and 29% (26/89) respectively. Two patients with BPDCN met the laboratory criteria for Hy’s Law; in both cases the laboratory abnormalities were noted during Cycle 1.

Haematological abnormalities

Thrombocytopenia was reported in 27% (60/225) of patients treated with ELZONRIS monotherapy and in 35% (31/89) of patients with BPDCN. Thrombocytopenia Grade ≥ 3 was reported in 20% (46/225) of patients treated with ELZONRIS monotherapy and in 26% (23/89) of patients with BPDCN. The majority of thrombocytopenia events were reported in cycle 1 and cycle 2 of treatment. Neutropenia was reported in 8% (17/225) of patients treated with ELZONRIS monotherapy and in 11% (10/89) of patients with BPDCN, with events ≥ Grade 3-reported in 5% (12/225) and 8% (7/89), respectively.

Hypersensitivity

Reactions representative of hypersensitivity were reported in 19% (42/225) of patients treated with ELZONRIS monotherapy and in 18% (16/89) of patients with BPDCN, with events ≥ Grade 3 reported in 3% (6/225) and 4% (4/89), respectively (see section “Warnings and precautions”).

Immunogenicity

Immune response was evaluated by assessment of serum binding reactivity against tagraxofusp (anti-drug antibodies; ADA) and neutralising antibodies by inhibition of functional activity. Immune response was assessed using two immunoassays. The first assay detected reactivity directed against tagraxofusp (ADA), and the second assay detected reactivity against the interleukin-3 (IL-3) portion of tagraxofusp. Two cell-based assays were used to investigate the presence of neutralising antibodies by inhibition of a cell-based functional activity.

In 241 patients treated with ELZONRIS in four clinical studies:

- 96% (216/224) of patients evaluable for the presence of pre-existing ADA at baseline before treatment were confirmed positive, with 27% being positive for the presence of neutralising antibodies. The high prevalence of ADA at baseline was anticipated due to diphtheria immunisation.
- 99% (204/205) of patients evaluable for treatment-emergent ADA tested positive, with most patients showing an increase in ADA titre by the end of Cycle 2 of ELZONRIS.
- 92% (155/169) of ADA-positive patients evaluable for the presence of neutralising antibodies post-treatment were neutralising antibody-positive.
- 76% (155/205) of patients evaluable for treatment-emergent anti-IL-3 antibodies tested positive, with most patients testing positive by Cycle 3 of ELZONRIS.
- 70% (109/155) of patients who tested positive for anti-IL-3 antibodies and were evaluable for the presence of neutralising antibodies were neutralising antibody-positive.

Paediatric population

The safety of ELZONRIS in children and adolescents has not been established. Limited data are available from case reports in patients aged 2-16 (mean age 15 years). No data are available for children less than 2 years of age.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported with ELZONRIS. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment provided immediately.

Properties/Effects

ATC code

L01XX67
Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents

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 targets CD123-expressing cells.

Pharmacodynamics

Tagraxofusp irreversibly inhibits protein synthesis of target cells by inhibiting elongation factor 2 (EF2), resulting in apoptosis (cell death).

Clinical efficacy

Study STML-401-0114 was a multi-stage (stage 1 dose escalation, stage 2 expansion, stage 3 confirmatory, stage 4 continued access), non-randomised, open-label, multi-centre study of ELZONRIS. ELZONRIS was administered to 65 previously-untreated and 19 previously treated adult patients with BPDCN according to the WHO classification, who received a 12 µg/kg dose on days 1-5 of multiple 21-day cycles.

The study enrolled 65 treatment-naïve patients. The mean age was 68 (range: 22, 84), 80% were male and 88% were white. 48% of patients had an ECOG performance status of 0, 48% had a value of 1, and 3% had a value of 2. The BPDCN characteristics at baseline were skin involvement for the majority (92%) of patients, followed by involvement of lymph nodes (51%), bone marrow (49%), peripheral blood (26%) and visceral (14%). Patients with known active or suspected CNS leukaemia as well as clinically significant cardiovascular disease were not included in the study.

The primary endpoint was a combination comprising the rate of complete remission (CR; complete resolution of the disease)/clinical complete remission (CRc; CR with residual skin abnormality not indicative of active disease). Across all 65 previously untreated patients ELZONRIS resulted in a CR/CRc rate of 56.9% (95% CI: 44.0, 69.2). This included 13 patients in the confirmatory efficacy cohort where the CR/CRc rate was 53.8% (95% CI: 25.1, 80.8). (Table 4).

Median overall survival (OS) in patients who received ELZONRIS and bridged to stem cell transplant was not reached (95% CI 18.9, NE). Median OS in patients not bridged to transplant was 9.0 months (95% CI 5.9, 12.0).

Table 4: Efficacy variables in patients with BPDCN treated with 12 µg/kg of ELZONRIS

	Treatment-naïve BPDCN	
Parameter	**Confirmatory cohort N=13**	**All cohorts N=65**
Response rate		
CR/CRc* Rate, N (%)	7 (54)	37 (57)
(95% CI)	(25.1, 80.8)	(44.0, 69.2)
Duration of CR/CRc (months)**		
Median	NE	24.9
Minimum, Maximum	3.9, 36.1	1.0, 57.4
Overall response rate, N (%)	10 (77)	49 (75)
(95% CI)	(46.2, 95.0)	(63.1, 85.2)
Bridge to stem cell transplant		
Rate, N (%)	6 (46)	21 (32)
(95% CI)	(19.2, 74.9)	(21.2, 45.1)
Overall survival		
Median	18.9 (5.2, NE)	15.8 (9.7, 25.8)
Minimum, Maximum	0.2, 38.7	0.2, 58.1

* CRc is defined as complete response with residual skin abnormality not indicative of active disease.
** Duration of CR/CRc includes patients bridged to stem cell transplantation.

Paediatrics

The efficacy of ELZONRIS in children and adolescents has not been established. Limited data are available from case reports of paediatric patients aged 2-16 (mean age 15 years). No data are available for children under the age of 2 years.

Pharmacokinetics

The pharmacokinetics of tagraxofusp has been evaluated in 43 patients with BPDCN. Most patients (n=38) had pre-existing anti-drug antibodies (ADA) against the diphtheria toxin (DT) component, due to previous vaccination. Pre-existing ADAs resulted in higher clearance and lower unbound tagraxofusp concentrations. During treatment, all patients developed high ADA titres, and substantially reduced free tagraxofusp levels (see below).

Following administration of ELZONRIS 12 µg/kg via 15-minute infusion in patients with BPDCN without pre-existing anti-drug antibodies (ADA, N=5), the mean (SD) unbound area under the plasma drug concentration over time curve ($AUC_{unbound}$) of free tagraxofusp on Day 1 of the first cycle of treatment (C1D1) was 230 (123) hr*µg/L and maximum unbound plasma concentration (C_{max}) was 162 (58.1) µg/L. In ADA positive patients AUC and C_{max} were 150 (89.1) hr*µg/L and 80.3 (81.1) µg/L, respectively.

Absorption

ELZONRIS is administered as an intravenous infusion.

Distribution

All data referred to below are based on free tagraxofusp concentrations in the first treatment cycle.

The mean (SD) volume of distribution of free tagraxofusp on C1D1 was 5.1 (1.9) L in 4 patients with BPDCN without pre-existing ADA and 21.2 (25.4) L in 25 ADA positive patients.

Metabolism

Tagraxofusp is expected to be degraded into peptides and its constituent amino acids through proteolysis, with no involvement of CYP or transporters.

Elimination

The mean (SD) clearance of free tagraxofusp at C1D1 was 7.1 (7.2) L/hr in 4 patients with BPDCN without pre-existing ADA, and the mean (SD) terminal half-life of tagraxofusp was 0.7 (0.3) hours. In ADA positive patients clearance was 13.9 (19.4) L/hr and half-life was 1.18 (0.6) hours.

Kinetics in specific patient groups

Due to the low unbound tagraxofusp concentrations, the effect of body weight, age, and gender could not be investigated.

Hepatic impairment

Due to the low unbound tagraxofusp concentrations, the pharmacokinetics of tagraxofusp in patients with hepatic impairment could not be investigated.

Renal impairment

Due to the low unbound tagraxofusp concentrations, the pharmacokinetics of tagraxofusp in patients with renal impairment could not be investigated.

Children and adolescents

The pharmacokinetics of tagraxofusp have not been studied in the paediatric population.

Pharmacokinetic/pharmacodynamic correlations

Data collected in cycle 3 showed increased ADA titres and significantly decreased concentrations of unbound tagraxofusp. However, clinical efficacy was also demonstrated after cycle 1 despite the lower exposure. The utility of concentrations of unbound tagraxofusp as a predictor of response is limited.

Preclinical data

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. These findings were generally noted after 5 days of daily dosing. 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, up to 3 weeks after dosing stopped.

Genotoxicity and Carcinogenicity

Carcinogenicity or genotoxicity studies have not been performed with tagraxofusp. Tagraxofusp is a recombinant protein and is therefore not expected to interact directly with DNA.

Reproductive toxicity

No fertility studies have been conducted with tagraxofusp. A literature-based risk assessment suggests that exposure to exogenous IL 3 or blockade of IL 3 signaling may have embryotoxic effects on foetal haematopoiesis and embryo-foetal development.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under “Instructions for handling”.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The preparation does not contain a preservative. For microbiological reasons, the medicinal product should be diluted and infused immediately after opening.

Shelf life after preparation of solution for infusion

The diluted preparation for infusion is not preserved. Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. For microbiological reasons, the product should be used immediately. If this is not possible, in-use storage times and conditions are the responsibility of the user.

Special precautions for storage

Store and transport frozen (-20°C ±5°C). [1]

Do not refreeze after thawing.

Keep the vial in the outer carton in order to protect from light.

Keep out of the reach of children.

Instructions for handling

General precautions

Procedures for proper handling, including personal protective equipment (e.g. gloves), and disposal of anti-cancer medicines should be followed.
The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Preparation and administration

Preparing the infusion

Ensure 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
- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Three 10 mL sterile syringes
- One 1 mL sterile syringe
- One mini-bifuse Y-connector
- Microbore tubing
- One 0.2 µm low protein binding polyethersulfone in-line filter

Use only if the solution is clear and colourless or with a few white to translucent particles.

Allow vials to thaw at not more than 25 °C or below for up to 1 hour in the outer carton. Do not refreeze a vial once thawed.

[1] Mod. 3.2.P.8.1 Stability Summary and Conclusion, 6. Labelled Storage Condition

Determining dosage amount

Calculation to determine the total ELZONRIS dose (mL) to be administered (see section "Dosage/Administration"):

$$\frac{\text{ELZONRIS dose (µg/kg) x patient's body weight (kg)}}{\text{Diluted vial concentration (100 µg/ml)}} = \text{Total dose (mL) to be administered}$$

A 2-step process is required for preparation of the final ELZONRIS dose:

Step 1 -prepare 10 mL of 100 µg/mL ELZONRIS

- Using a sterile 10 mL syringe, transfer 9 mL of sodium chloride 9 mg/mL (0.9%) 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 9 mL of sodium chloride 9 mg/mL (0.9%) 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 µg/mL.

Step 2 – Prepare the ELZONRIS infusion set

- Calculate the required volume of diluted ELZONRIS (100 µg/mL) according to patient's weight.
- Draw up the required volume into a new syringe (if more than 10 mL of diluted ELZONRIS (100 µg/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 sodium chloride 9 mg/mL (0.9%) solution for injection to be used to flush the administration set once the ELZONRIS dose is delivered.
- Label the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe.
- Connect the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe to one arm of the Y-connector and ensure the clamp is closed.
- Connect the product syringe to the other arm of the Y-connector and ensure the clamp is closed.
- Connect the terminal end of the Y-connector to the microbore tubing.
- Remove the cap from the supply side of the 0.2 µm filter and attach it to the terminal end of the microbore tubing.
- Unclamp the arm of the Y-connector connected to the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe. Prime the Y-connector up to the intersection (do not prime the full

infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection). Re-clamp the Y-connector line on the sodium chloride 9 mg/mL (0.9%) solution for injection flush arm.

- Remove the cap on the terminal end of the 0.2 µm filter and set it aside. Unclamp the arm of the Y-connector connected to the product syringe, and prime the entire infusion set, including the filter. Recap the filter, and re-clamp the Y-connector line on the product side. The infusion set is now ready for delivery for dose administration.

The diluted solution should be used immediately once prepared.

Administration

1. Establish venous access and maintain with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
2. Administer the prepared ELZONRIS dose via infusion with an infusion syringe pump over 15 minutes. The total infusion time will be controlled using an infusion syringe pump to deliver the entire dose and the sodium chloride 9 mg/mL (0.9%) solution for injection flush over 15 minutes.
3. Insert the ELZONRIS syringe into the infusion syringe pump, open the clamp on the ELZONRIS side of the Y-connector and deliver the prepared ELZONRIS dose.
4. Once the ELZONRIS syringe has been emptied, remove it from the pump and place the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe in the infusion syringe pump.
5. Open the clamp on the sodium chloride 9 mg/mL (0.9%) solution for injection flush side of the Y-connector and resume infusion via the infusion syringe pump at the pre-specified flow to push the remaining ELZONRIS dose out of the infusion line to complete delivery.

Disposal

ELZONRIS is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68797 (Swissmedic)

Packs

ELZONRIS 1 vial containing 1 mL concentrate with 1 mg tagraxofusp (A)

Marketing authorisation holder

Stemline Therapeutics Switzerland GmbH, Zug

Date of revision of the text

November 2022