12 November 2020
EMA/CHMP/24699/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elzonris

International non-proprietary name: tagraxofusp

Procedure No. EMEA/H/C/005031/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug (tagraxofusp) antibody
ADR	Adverse drug reaction
AE	Adverse event
AIA	Anti-human interleukin-3 antibody
allo-SCT	Allogeneic hematopoietic stem cell transplantation
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
auto-SCT	Autologous hematopoietic stem cell transplantation
BLA	Biologics License Application
BM	Bone marrow
BPDCN	Blastic plasmacytoid dendritic cell neoplasm
C	Cycle
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CLS	Capillary leak syndrome
Cmax	Maximum concentration
CR	Complete response
CRc	Complete response with minimal residual skin abnormality
CRi	Complete response with incomplete blood count recovery
CSR	Clinical study report
D	Day
DOR	Duration of objective response
DT	Diphtheria toxin
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IL-3	Interleukin-3
IL-3R/CD123	Interleukin-3 receptor
IND	Investigational New Drug Application
MedDRA	Medical Dictionary for Regulatory Activities

NAb	Neutralizing antibody
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
pDCs	Plasmacytoid dendritic cells
PFS	Progression-free survival
PR	Partial response
QTcF	Heart rate-corrected QT interval using Fridericia's correction
RFS	Relapse-free survival

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TMC Pharma (EU) Limited submitted on 7 January 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Elzonris, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 March 2018.

Elzonris, was designated as an orphan medicinal product EU/3/15/1567 on 11 November 2015 in the following condition: Treatment of blastic plasmacytoid dendritic cell neoplasm.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Elzonris an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/elzonris

The applicant applied for the following indication: Elzonris is indicated for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0326/2018 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active substance status

The applicant requested the active substance tagraxofusp contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 June 2015	EMA/CHMP/SAWP/384630/2015	Dr Hans Ovelgönne and Dr Jan Sjöberg
20 July 2017	EMA/CHMP/SAWP/431942/2017	Dr Serena Marchetti and Dr Karl-Heinz Huemer

The Protocol assistance pertained to the following *non-clinical and clinical* aspects:

- *The plan to support the dosage form change for use of lyophilised drug product*
- *The adequacy of the non-clinical studies to support licensure*
- *Concurrence that blastic plasmacytoid dendritic cell neoplasm constitutes an orphan population and that a single uncontrolled pivotal trial would be acceptable to support a MAA*
- *The design of the pivotal trial STML-401-0115 in patients with relapsed or refractory BPDCN, in terms of population, dose, endpoints, criteria for measurement of tumour response, sample size, statistical analysis plan*
- *The design of study STML-401-0114 in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)*
- *Concurrence that a meaningful rate of complete response would support a MAA in the first-line treatment of BPDCN patients*
- *Concurrence with ORR as the main endpoint for analysis of efficacy for patients with relapsed/refractory BPDCN*
- *Descriptive nature of the data analyses as well as pooling of data from patients enrolled across all stages of study STML-401-0114 for the R/R BPDCN population*
- *The safety database at MAA*

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Bjorg Bolstad

The appointed rapporteurs had no prominent role in Protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	7 January 2019

Accelerated Assessment procedure was agreed-upon by CHMP on	15 November 2018
The procedure started on	25 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	27 March 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	26 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 April 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 May 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	13 June 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 March 2020
The procedure was reverted to a standard timetable on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 June 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 June 2020
SAG/Expert group/ Working Party experts (as appropriate) were convened to address questions raised by the CHMP on	05 March 2020

The CHMP considered the views of the SAG/Expert group/ Working Party (as appropriate) as presented in the minutes of this meeting.	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Elzonris on	23 July 2020

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Filip Josephson

The appointed co-rapporteur had no prominent role in Protocol assistance relevant for the indication subject to the present application.

The applicant submitted written notice to the EMA, to request a re-examination of Elzonris CHMP opinion of 23 July 2020, on	5 August 2020
The CHMP appointed Janet Koenig as Rapporteur and Filip Josephson as Co-Rapporteur on	20 August 2020
The applicant submitted the detailed grounds for the re-examination on	16 September 2020
The re-examination procedure started on	17 September 2020
The Rapporteur's re-examination assessment report was circulated to all CHMP members on	23 October 2020
The Co-Rapporteur's assessment report was circulated to all CHMP members on	19 October 2020
The Rapporteurs circulated the Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	4 November 2020
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting	4 November 2020
The detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP on	10 November 2020
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation under exceptional circumstances on	12 November 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematologic malignancy characterized by the clonal proliferation of malignant plasmacytoid dendritic cells. In 2008, BPDCN was classified by the World Health Organization (WHO) as a distinct entity in the group of "acute myeloid leukaemia (AML) and related precursor neoplasms".

2.1.2. Epidemiology and risk factors, screening tools/prevention

The prevalence estimate for BPDCN in line with the information presented for the EU orphan designation application is 1.2 per 10,000. The true incidence and prevalence of BPDCN, like many other rare diseases without definitive and/or effective therapy, is not precisely known. However, based on a published report (Wang, 2012), BPDCN may constitute approximately 0.44% of haematologic cancers annually, or approximately 700 and 1000 incident cases annually in the US and Europe, respectively.

2.1.3. Biologic features/Aetiology and pathogenesis

BPDCN is a rare and aggressive haematodermic neoplasm, which typically occurs in elderly patients, with a mean age between 60 and 70 years; however, the disease may present at any age. BPDCN is more prevalent in males, with a male to female ratio of 3:1. Typically, the malignant cell in BPDCN has abundant cytoplasm with a medium or low nucleus-to-cytoplasmic ratio and displays faint basophilia without granulation. However, microvacuoles are commonly seen, most likely made of glycogen, arranged in a way to adopt a "pearl necklace" aspect beneath the nuclear membrane and characteristic pseudopod-like cytoplasmic expansions. Malignant cells of BPDCN generally coexpress CD4+ and CD56+ without coexpressing common lymphoid or myeloid lineage markers. However, in some cases of BPDCN cells express myeloid markers (CD33), suggesting that CD33 expression on CD4+ and CD56+ cells should not exclude such diagnoses.

Several cases of BPDCN showed coexpression of CD2, CD7, CD33, and/or CD117. Identified key markers include CD123, the interleukin-3 receptor a-chain, T cell leukaemia/lymphoma 1 (TCL1), blood dendritic cell antigen-2 (CD303/BDCA-2), and CD2- associated protein (CD2AP). CD2AP appears to be restricted to plasmacytoid dendritic cells, potentially making it a useful tool to confirm the diagnosis of BPDCN.

Recurrent reciprocal chromosomal translocations or inversions, as are common in acute leukaemias or mature lymphoid neoplasms, have not been identified in BPDCN. Instead, karyotypic analysis often shows complex aberrations similar to those seen in MDS or AML arising from MDS. No single defining genetic abnormality is described, but, by far, the most frequently observed is deletion 5q (up to 72% of cases), followed in decreasing frequency by alterations of 13q, 12p, and 6q and losses of chromosomes 15 and 9.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The disease has a proclivity to involve the skin, bone marrow, and lymph nodes. Up to 90% of patients have asymptomatic solitary or multifocal skin lesions that can be nodules or patch-plaque or bruise-like areas that measure from a few millimetres to up to 10 cm. Associated erythema, hyperpigmentation, purpura, and ulceration can be seen. In nearly 50% of cases, the skin lesions are the only detectable extramedullary tumour manifestation. LN involvement at presentation is common (40%-50%), but splenomegaly (~20%) or involvement of other mucosal sites (~10%) is relatively infrequent. Systemic B symptoms are rare at diagnosis. Low-level BM and peripheral blood (PB) involvement are seen in most cases (60%-90%); however, initial fulminant leukaemia is rare (5%-25%). Fulminant leukaemia is a common feature of HDT progression or relapse and is nearly always present in the terminal stage.

The diagnosis of BPDCN is based on a constellation of clinical features, morphologic findings, and cytogenetic and molecular data. BPDCN exhibits a specific immunophenotype and coexpresses CD4, CD43, CD45RA, and CD56 as well as pDC-related antigens, including CD123 (interleukin 3α chain receptor), T-cell leukaemia 1 (TCL1), cutaneous lymphocyte-associated antigen, blood dendritic cell antigen (BDCA) 2 (CD303), BDCA4/CD304, CD2AP, Spi-B transcription factor, and platelet endothelial cell adhesion molecule (CD31). The median overall survival observed in BPDCN is 12 to 16 months, irrespective of the initial pattern of disease. Advanced age is an adverse prognostic factor.

2.1.5. Management

There are no medicines specifically authorised for the treatment of BPDCN and no standard of care treatment has been established for patients with newly-diagnosed (first-line) or previously-treated (relapsed/refractory) disease.

Because of the rarity of BPDCN, no prospective data are available to define the most optimal frontline therapy. Clinical practice varies based on institutional preference. Limited cutaneous disease at presentation, without obvious nodal, bone marrow, and/or peripheral blood involvement, is not uncommon. However, even in such cases, local therapies (e.g., surgical excision or involved field radiation therapy) are ineffective, with systemic relapse anticipated in almost all cases, typically within 6 months.

According to limited retrospective reviews, empirical therapies historically employed to treat patients with treatment-naïve BPDCN generally were those, or modified versions of those, used for aggressive haematologic malignancies, including lymphoma (e.g. cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or CHOP-like), AML (e.g. cytarabine plus an anthracycline), or acute lymphoblastic leukaemia (ALL) (e.g. cyclophosphamide, vincristine, doxorubicin, dexamethasone, [hyper-CVAD] alternating with methotrexate, and cytarabine).

Feuillard et al treated 23 patients with CHOP-like regimens and reported a complete response (CR) rate of 86%; however, responses were short lived, with a median time to relapse of 9 months. More intensive, ALL-like treatment regimens (e.g., hyper-CVAD) yielded higher response rates. Pemmaraju et al reported a CR of 90% in 10 patients treated with hyper-CVAD, reporting a median duration of response of 20 months and a median overall survival rate of 29 months (Kharfan-Dabaja, 2013). AML-like treatment regimens have also been used as initial therapy. Dietrich et al reported a CR rate of 83% in 6 patients treated with an AML-like regimen.

BPDCN patients should be referred for an allo-HCT evaluation as soon as possible to determine their candidacy for the procedure and to initiate donor identification in eligible cases. If a suitable human leukocyte antigen compatible donor is identified, allo-HCT should be considered in patients in first CR, which appears to be a prerequisite for long term durable remissions. Auto-HCT could be offered in the

setting of chemosensitive disease, preferably early in the disease course if a suitable donor is not available. This represents an important treatment algorithm to consider due to relatively short-lived remissions after frontline therapies and because effective second-line therapies remain elusive.

About the product

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

The sponsor applied for the following indication: Elzonris is indicated for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

During the evaluation the applicant revised the proposed indication as follows: Elzonris is indicated as monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (see section 5.1).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the CHMP considered that the product could be of major public health interest. This was based on the results of overall survival associated with manageable safety as presented by the applicant. Indeed, no therapy for BPDCN is considered the standard of care, given the low incidence of this disease and poor durability of responses for most strategies used to date.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the nature/complexity of the quality MOs remaining at D90 did not fit into the accelerated procedure anymore and a normal timetable for assessment was therefore required. In addition, request for SAG consultation could not fit into the accelerated assessment timetable.

The application was submitted by TMC Pharma (EU) Limited; during the procedure the applicant was changed to Stemline Therapeutics B.V.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 1 mg/mL of tagraxofusp as active substance.

Other ingredients are trometamol, sodium chloride, sorbitol (E420) and water for injections.

The product is available in type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 1 mL concentrate.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active Substance

General information

The active substance (international nonproprietary name: tagraxofusp) is a 524-amino acid, recombinant non-glycosylated fusion protein expressed in an *Escherichia coli* cell line. from a hybrid gene comprised of the deoxyribonucleic acid (DNA) sequence of human interleukin-3 (IL-3) contiguous with a truncated version of diphtheria toxin (DT) intentionally engineered without its receptor binding domain, since the IL-3 replaces the DT receptor binding domain.

MGADDVVDSSKSFVMENFSSYHGTKPGYVDSIQKGIQKPKSGTQGNYDDDW
KGFYSTDNKYDAAGYSVDNENPLSGKAGGVVKVTYPGLTKVLALKVDNAE
TIKKELGLSLTEPLMEQVGTEEFIKRFGDGASRVVLSLPFAEGSSSVEYINNW
EQAKALSVELEINFETRGKRGQDAMYEYMAQACAGNRVRRSVGSSLSCINL
DWDVIRDKTKTKIESLKEHGPIKNKMSESPNKTVSEEKAKQYLEEFHQTAL
EHPELSELKTVTGTNPVFAGANYAAWAVNVAQVIDSETADNLEKTTAALSIL
PGIGSVMGIADGAVHHNTEEIVAQSIALSSLMVAQAIPLVGELVDIGFAAYNF
VESIINLFQVVHNSYNRPAYSPGHKTRP*HM*APMTQTTSLKTSWVNCSNMIDEII
THLKQPPLPLLDFNNLNGEDQDILMENNLRRPNLEAFNRAVKSLQNASAIESILK
NLLPCLPLATAAPTRHPIHIKDGDWNEFRRKLTFYLKTLENAQAQQTTLSLAIF

Figure 1: Protein sequence of tagraxofusp

Tagraxofusp is therefore composed of human interleukin-3 (IL-3) and truncated diphtheria toxin that inhibits protein synthesis and induces apoptosis in cells expressing the interleukin-3 receptor (IL-3R). The tagraxofusp protein consists of an N-terminal methionine, followed by the first 388 amino acids of DT comprising the catalytic and translocation domains. The DT fragment (Q388R variant) is genetically fused at the C-terminus through a His-Met dipeptide linker to the N-terminus of the full 133-amino acid sequence of human IL-3. Two disulphide bonds are present and no free cysteines are observed.

The molecular weight of tagraxofusp based on the amino acid sequence is 57,695.1 Dalton. The molecular formula of tagraxofusp is $C_{2553}H_{4026}N_{692}O_{798}S_{16}$.

Control of materials

Acceptable information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Detailed descriptions of consumables such as resins and filters are presented. Leachables and extractables for single-use material are discussed further below. For material containing, or coming into contact with, animal-derived components, an evaluation and a TSE/BSE statement is included in the dossier and found satisfactory.

The tagraxofusp expression system is based on *E. coli* BLR(DE3). Construction of the plasmids used to generate the initial cell clones, transfection of cells and selection of the producing clone were sufficiently described, as well as the strategy leading to the selection of the final RCB.

A two-tiered cell bank system was established for commercial production. The banking procedure was adequately described and qualified in accordance with ICH Q5D guideline. The cell banks are stored at multiple locations.

The information regarding the host cell and the vector is sufficient and the approach for manufacture and testing of the master cell bank (MCB) and working cell bank (WCB) is supported. Tests performed on MCB and WCB include: detection of bacteriophage, cell viability, retention of expression construct, sequencing of recombinant plasmid expression vector, plasmid analysis by restriction mapping, purity by complex media and gram stain and identity by analytical profile index and gram stain. No animal-sourced materials were included in the manufacture of the MCB or the WCB although animal-derived tryptone was used in the culture medium for the pre-Research Cell Bank (RCB).

The proposed stability testing of the MCB and the WCB (analyses and intervals) is acceptable.

The proposed approach taken to define the limit of *in vitro* cell age, LIVCA, is supported. End of production cells are appropriately prepared, characterised and tested. Genetic stability has been appropriately demonstrated.

There is no protocol for the establishment of future WCBs in the dossier. The applicant confirms that manufacture and testing of future WCBs will be applied for via post-approval variation application.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the tagraxofusp active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process parameters that impact critical quality attributes (CQAs) and need to be controlled in a relatively narrow range are defined as critical process parameters (CPPs), this is endorsed since in line with ICH Q8(R2).

Process validation

The tagraxofusp active substance manufacturing process has been validated adequately at the commercial site. Consistency in production has been shown on four full scale commercial batches manufactured using the commercial process. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces tagraxofusp active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

During manufacturing process development, four active substance manufacturing processes were used: A, B1, B2 and C. During manufacturing process development, several manufacturing processes were used. The CHMP raised a major objection on information relating to comparability of manufacturing processes. Additional information was then provided and the major objection was resolved.

Due to the limited clinical exposure using commercial process/batches and non-compliance to ICH Q5E, the abbreviated comparability study presented was not accepted and major objections were raised by CHMP during the assessment.

Additional information was then provided to support the comparability between processes B1/B2 and process C batches. As an overall conclusion, the data provide support the claim that process C material is comparable to process B1/B2 material and the major objection was resolved.

The applicant proposes a control strategy approach based on quality risk management principles.

The proposed approach to establish the process control strategy does not fully correspond to the ICH Q8 requirements since the QTPP profile and the list of CQA were established after process characterisation and process validation studies. A major objection was raised asking for a justification of the control strategy. In order to resolve the major objection, the applicant confirmed that proven acceptable ranges' (PARs) parameters will be varied (that is, adjusted within approved ranges) one at a time only and additional tests are added as process parameters or in-process controls. This is considered acceptable.

The applicant confirms that the proposed approach for this application is a traditional approach and not a QbD filing. However, QbD elements such as risk assessment and multivariate experimental design were used during process characterisation. Results from multivariate and univariate experiments were used to evaluate process parameter criticality. According to the narrative, the process parameter acceptable ranges were confirmed rather than defined, by the process characterisation.

Process characterisation studies were performed to ensure acceptable process performance and product quality from the design and operating space around NORs. The strategy to use multivariate understanding to increase process knowledge and establish ranges for process parameters is supported. It is also acknowledged that a multivariate process characterisation does not necessarily lead to a multivariate manufacturing description and control. The multivariate models used to gain knowledge about significant effects of process parameters on attributes are now sufficiently described but the model validities and goodness-of-fits have not been submitted. It is agreed that the fit of the models is not as important when the main use is that of assessment of parameter criticality rather than prediction. The fact that the model validities are not submitted, and that it was not possible to evaluate process parameter interactions for several steps leads to the conclusion that process parameters should only be allowed to vary (that is, adjusted within approved ranges) one at a time within the proposed ranges.

It is noted that the characterised ranges in general are quite narrow, which probably is one reason as to why only few effects with practical significance are found.

The process characterisation results are presented in extensive tables with parameter and attribute classification, acceptable operating ranges (AORs) and NORs, and rationales. The presentation and defined parameter and attribute limits are approvable, considering that additional CQAs, CPPs, Key Process Parameters (KPPs) and Key Process Attributes (KPAs), have been added to the control strategy.

Characterisation

State-of-the art methods were applied to characterize the primary, secondary and tertiary structure and various physicochemical properties of tagraxofusp.

Process-related impurities

Process-related impurities were shown to be removed to low levels by the purification process as discussed for process validation (PV) batches and spiking studies performed during development studies.

Specification

The active substance release specifications are presented. They include tests for identity, strength, potency, purity, safety and general properties.

The proposed release and shelf-life specifications cover the relevant characteristics of the protein and appropriate stability-indicating analytical procedures are established to monitor and assess the degradation patterns of the protein.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The potency is determined using a bioassay.

During the procedure a major objection was raised on the adequacy of the potency method validation. A detailed review of the current cell-based cytotoxicity assay was conducted leading to a re-development effort to optimize method performance and to address a number of factors that contribute to variability. The method has been revised and a full re-validation performed and considered acceptable, resolving the major objection.

An updated method description and a summary of the re-validation of the method is provided. An investigation was performed in order to explain the observed bias between the two versions (former and current) of the cell-based cytotoxicity assay. The bias initially observed was not confirmed by the new testing which was performed for each sample using individual reference standards for each assay. The proposed explanation is endorsed.

A receptor binding test method was introduced upon CHMP's request.

As requested, acceptance criteria are now included in the active substance specification and are considered acceptable. The method summary and the validation of this new assay raise several outstanding points. An ongoing investigation is performed to explain the observed overall lower receptor binding activity of the active substance and the finished product relative to reference material. The update of the results of the ongoing investigation is not available until January 2021. Potential impact of the conclusions of this investigation should be considered for active substance and finished product release and shelf life specifications for receptor binding. The applicant proposes to discuss a potential revision of the active substance and finished product release and shelf life specifications via a post-approval variation. This is supported and the current method is deemed suitable for authorisation with the commitment to improve the method (listed as a recommendation for a future quality development).

Batch analysis

Batch analysis data on 7 pilot scale and 5 commercial scale batches of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Batch data for the active substance were presented for Process B1, Process B2 and Process C batches.

Reference materials

The history of the three reference standards used during development was described and is comprehensive.

Data was evaluated with equivalence testing for changes in reference standards. And the results are acceptable.

A protocol for qualification of new reference material is submitted. It was used for qualification of a new WRS and it has been confirmed that this protocol will be used for future WRS as well.

Stability

The applicant proposes a commercial shelf life for tagraxofusp active substance of 36 months at the recommended long-term storage condition of -70°C ± 10°C.

The container closure material is identical to the active substance container closure, except for the smaller volume and considered representative of commercial closure.

Shelf life specifications have been revised during process development. The currently proposed shelf life specifications are the same as the proposed commercial active substance release. The chosen analytical methods are adequately stability indicating.

As requested by CHMP, real-time receptor binding stability results have been reported for active substance batches and demonstrate that the acceptance criteria are fulfilled.

All future stability protocols will include potency assessment via the current cytotoxic potency assay and receptor binding. Additionally, the method will be added to future timepoints for ongoing stability studies. The applicant commits to continue the ongoing stability studies until completion and to report out-of-specification stability results to the authorities. This is endorsed.

The stability results indicate that the active substance is sufficiently stable and justifies the proposed shelf life in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a concentrate for solution for infusion presented as a single use, sterile aqueous solution at a concentration of 1mg/mL. The excipients are typically used for formulating this kind of product. The product is presented as a 1 mL solution in a 2 mL vial.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. No excipients of human or animal origin are used in the manufacture of the finished product. No formula overages are included.

The container closure system consists of a 2 mL glass vial, a 13 mm butyl rubber stopper and a flip-off seal. The development of the primary container closure system is sufficiently described and appropriate extractable/leachables studies were performed and do not raise any safety concern.

The formulation steps are performed during the finished product manufacturing process. An acceptable overview is provided on the development of the formulation, including satisfactory data supporting the proposed composition of the commercial finished product.

Throughout development, visual inspection of the finished product revealed the presence of proteinaceous product-related particles. A major objection was raised requesting more information on the source and nature of visible particles. The proteinaceous nature of these visible particles seemed to be demonstrated however, additional silicone was observed during the particle studies. The silicon observed during the particle studies was investigated and determined to have been introduced to the finished product samples used for this study primarily from the use of siliconized stoppers used during

manufacturing at the initial contract manufacturer during development. While other single-use components used during manufacturing also contain silicon, the transient nature/short duration of contact was deemed to be less likely to result in silicon contamination in the product.

Since transfer of the process to the current contract manufacturer in 2014, non-siliconized stoppers, the same as the proposed commercial container closure system, have been used.

Silicon levels for aged finished product were assessed as part of the extractable/leachable study. From this study, silicone oil was not found in the aged finished product. A long-term leachable study is ongoing, with no levels of concern reported through 12 months of testing to date. After transfer to another manufacturing site, it is clear that silicone is no longer an issue. The applicant indicates that visible particles are removed prior to dose administration by an in-line 0.2 µm filter used during administration (not supplied). The studies performed in order to demonstrate the nature of observed particles and all the data regarding the formulation studies performed to reduce or remove visible particulate matter have been provided and found acceptable. Moreover, the specification limit has been changed. This is deemed acceptable and sufficient to resolve the major objection. The capacity of the in-line filter (polyethersulfone) to remove these proteinaceous particles and its compatibility with the finished product is appropriately demonstrated. No loss in potency nor of protein was observed.

During manufacturing process development, two major modifications were introduced. The first modification was introduced early in the development, it consisted of the change from process A to process B, including the change of the manufacturing site and introduction of improvements during the manufacturing process. Comparability between process B batches and process B batches is provided and batches are demonstrated to be comparable.

Regarding process characterisation, the same approach as the one used for the active substance was proposed for the finished product. A risk analysis was performed, and results of the process characterisation studies were used to set the NORs and PARs for the process parameters. The ranges proposed in the description of the manufacturing process are acceptable and will ensure consistency of the manufacturing process. Discrepancies observed between the manufacturing process development and the description of the manufacturing process sections are discussed and additional controls have been added to the manufacturing process.

A compatibility study was performed with the finished product after dilution in 0.9% NaCl solution to a concentration of 0.1 mg/mL. The aim of the in-use study was to demonstrate compatibility of the product with the diluent, an intravenous tubing set, syringes, and a terminal in-line filter used in the clinical administration of this product during 4 hours at ambient temperature. Protein recovery and potency were determined to demonstrate the compatibility of the dilution and material with the finished product. The additional compatibility study addressed the reduction of the visible particles and the compatibility of the finished product with the in-line filter.

Manufacture of the product and process controls

The finished product manufacturing process consists of several steps corresponding to: bulk active substance (BAS) thaw, Tris buffer preparation, sodium chloride/sorbitol diluent preparation, compounding of bulk solution, sterile filtration, filling, stoppering, sealing and inspection. The finished product is released for the EU market at MIAS Pharma Ltd., Ireland. During the procedure a major objection was raised on missing information regarding the Baxter Oncology GmbH, Germany and Charles River Laboratories Germany GmbH, Germany quality control testing laboratories. The missing information including GMP certificates for both sites were provided and the major objection resolved.

All finished product manufacturing sites are GMP-authorised for the relevant activities. The finished product vials are stored at -20°C ± 5°C

Acceptable ranges for process parameters are considered the normal operating ranges (NORs). In addition, acceptance criteria are established for the process controls (IPC/IPT). These acceptance criteria are acceptable as they manage to obtain a consistent and reproducible manufacturing process as regards the process validation data provided.

The definition of the CPPs is not in line with ICHQ8(R2), where a PP having an impact (even low impact) in a CQA, is considered as a CPP. Only one process parameter, mixing time at the mixing of bulk compounded solution step, has been identified as critical (CPP). However, the applicant's approach is accepted since both process parameters (CPP and non-CPP) are controlled on a routine basis. Two IPC are identified at the filtration step: the pre-filtration bioburden prior to the sterile filtration step and the filter integrity post sterile filtration step.

The manufacturing process controls have been updated to include an integrity test of the sterilising filters prior to use.

The process validation studies described in the dossier comprise finished product process validation, sterilisation process validation, filter validation and transport validation.

The validation studies included mainly the process parameter and process control results. The results met the NOR/PAR established based on the process characterisation studies and the proposed acceptance criteria. The overall validation of the finished product manufacturing process demonstrates that the process is consistent throughout the different steps.

Vials and stoppers are washed and sterilised at the finished product manufacturing site. Validation data are provided for the depyrogenating oven and the autoclave. This is found acceptable.

Results from filter validation of the PVDF sterilising filter are presented including results for microbial retention capacity. An in-use simulation exposure study was performed on the sterilising filter to investigate potential leachables. There were no extractable and leachable compounds from the filter that would pose any safety concern. For the 24-hour compatibility study, no visible changes to the filter were observed and the filter integrity testing met the requirements. No sorption of the solution during the finished product sterile filtration step was observed

Results from transport validation studies have been presented both for "bulk vial" and "end-customer". Controls will be in place to ensure the transport times and temperatures are monitored. The studies have been performed using water as simulated finished product, this is found acceptable since the study focused on the ability to maintain the frozen state.

Product specification

The finished product specifications include tests for identification, strength, potency, purity, safety and general properties.

The new receptor binding method was introduced in the finished product specification. During the procedure, appropriate acceptance criteria for the Receptor binding assay have been proposed and accepted.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

It is recommended (quality recommendation) that an updated risk evaluation on the potential presence of nitrosamine impurities in Elzonris (tagraxofusp) is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

No new impurities are introduced as a consequence of finished product manufacture or storage.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The non-compendial methods used to determine strength, potency and purity are identical to the active substance analytical methods.

Batch analysis

Batch analysis data on 11 finished product batches including 4 PPQ batches were provided. Results were within the acceptance criteria and confirm consistency of the manufacturing process. These data also demonstrate consistency and reproducibility of the manufacture across the 2 different processes.

Reference materials

The working reference standard used for testing and release of tagraxofusp finished product is the same as the one used for the active substance.

Stability of the product

A shelf-life of 2 years when stored at the recommended temperature of -20°C ± 5°C is proposed for the finished product.

Stability finished product lots were packaged in a container closure system representative of the commercial one. The analytical procedures used in stability-monitoring program are the analytical procedures used for batch analysis.

Since comparability between active substance processes B and C has been sufficiently demonstrated, the finished product stability data provided for Process B to date is found acceptable and supportive.

All future stability protocols will include potency assessment via the current cytotoxic potency assay. Additionally, the method will be added to future timepoints for ongoing stability studies presented in the dossier.

Based on the available stability data, a shelf-life of 2 years when stored in the outer carton, at the recommended temperature of -20°C ± 5°C is acceptable.

Adventitious agents

The active substance, tagraxofusp protein is a fusion protein manufactured via microbial fermentation utilizing recombinant *E. coli* host cells. The data provided are satisfactory concerning the viral adventitious aspect.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

During the procedure five major objections were raised on the quality aspects and GMP aspects (comparability of active substance manufactured with the proposed commercial process and active substance used for clinical trials, control strategy, presence of trace amounts of visible particles observed in the finished during development and the potency method). Data have been submitted by the applicant during the procedure in relation to these MOs and the CHMP has considered that these data is acceptable to resolve them.

One commitment remains regarding the assessment of the outstanding issues:

The update of the results of the ongoing investigation to explain the observed overall lower receptor binding activity relative to reference material is still outstanding and is not available until January 2021. The data should be provided as indicated. Potential impact of the conclusions of this investigation should be considered for active substance and finished product release and shelf life specifications for receptor binding. The applicant proposes to discuss a potential revision of the active substance and finished product release and shelf life specifications via a post-approval variation. This is supported. A complete commitment should be provided and this issue is put forward as a quality recommendation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

The update of the results of the ongoing investigation to explain the observed overall lower receptor binding activity of commercial active substance and finished product relative to reference material should be provided. Potential impact of the conclusions of this investigation should be considered for active substance and finished product release and shelf life specifications for receptor binding via a post-approval variation.

It is recommended that a risk evaluation on the potential presence of nitrosamine impurities in Elzonris (tagraxofusp) is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

The applicant has provided several published studies where tagraxofusp cytotoxic effects have been evaluated.

Table 1 and Table 2 describe *in vitro* and *in vivo* studies, respectively.

Table 1. *In vitro* studies of Tagraxofusp in BPDCN and AML

Type of assay	Test system reference	Main findings
Receptor binding assay	Binding of tagraxofusp to human and mouse CD123 by surface plasmon resonance Tagraxofusp (lot B160279) (Stemline Therapeutics, 2018)	Tagraxofusp bound selectively to human IL-3Rα (**Kd=470 nM**) and not to mouse IL-3Rα, likely due to the low amino acid sequence homology between human and mouse IL-3.
	Cold competition of unlabelled tagraxofusp and ^{125}I-labeled IL-3 variant for binding to TF/H-ras cells (Urieto, 2004)	Tagraxofusp has high affinity for the human IL-3R (**Kd=1.5 ± 0.7 nM**).
ADP-ribosylation assay	Activity assay measuring tagraxofusp-mediated incorporation of radiolabel from [^{14}C]-NAD+ to EF-2 in rabbit reticulocyte lysates (Urieto, 2004)	The ADP-ribosylation activity of tagraxofusp AT-1 and AT-2 batches is similar to that of DT388GM-CSF.
Cell viability / apoptosis assay	^{3}H-thymidine incorporation assay on human AML TF/H-ras cells (Urieto, 2004)	Tagraxofusp is cytotoxic against TF/H-ras cells (IC50 values of **6.1 pM and 8.7 pM** for AT-1 and AT-2, respectively).
	Flow cytometry with Annexin-V/PI staining of AML cells (Testa, 2005)	Tagraxofusp induces apoptosis in leukemic blasts from AML patients. Percentage of apoptosis was proportional to the relative expression of the IL-3R components on the patient samples.
	MTT assay (Stephansky, 2017)	DPH1, an enzyme involved in the conversion of His715 to diphthamide on EF-2 is a biomarker of acquired resistance to tagraxofusp and that downregulation of DPH1 expression is sufficient to mediate in vitro tagraxofusp resistance in BPDCN and AML cell lines. Furthermore, tagraxofusp resistance is reversible by azacytidine, suggesting that downregulation of DPH1 expression occurs through reversible promoter cytidine-phosphate guanosine DNA methylation.
	Flow cytometry with Annexin-V/PI or 7-AAD staining of AML cells (Mani, 2018)	Tagraxofusp induces apoptosis in leukemic blasts from patients with AML in a dose- and time-dependent manner. In vitro treatment with tagraxofusp did not markedly reduce CD123 expression on primary AML blasts
	Flow cytometry using fluorescein isothiocyanate-conjugated Annexin V and 7-aminoactinomycin D (7-AAD) staining of BPDCN (Angelot-Delettre, 2015)	Tagraxofusp reduced GEN2.2 and CAL-1(BPDCN patient-derived cell line) cell viability in a dose-dependent manner, with **IC50 values in the low femtomolar range**. Primary BPDCN cells obtained at relapse after chemotherapy retained their sensitivity to tagraxofusp as compared with cells obtained at time of diagnosis likely due to continued expression of CD123 at both diagnosis and relapse. BPDCN cells were more sensitive to tagraxofusp exposure than were cells from patients with AML or ALL.

Tagraxofusp binds to the human IL-3R with high affinity (Urieto, 2004), and this binding is specific to human CD123 but not to mouse CD123 (Stemline Therapeutics, 2018). The cytotoxic activity of tagraxofusp stems from its ability to inactivate EF-2 through ADP-ribosylation (Urieto, 2004) and induce apoptosis in CD123-expressing cells (Testa, 2005; Mani, 2018). Tagraxofusp exhibits antitumor activity against both BPDCN and AML cell lines and primary patient cells in vitro, with half maximal inhibitory

concentration (IC50) values against BPDCN cells in the femtomolar to picomolar range (Angelot-Delettre, 2015; Mani, 2018).

Table 2. *In vivo* studies of Tagraxofusp in BPDCN and AML

Type of Study, Study reference	Tumor cells	Dose and regimen	Main findings
NSG Mouse (Angelot-Delettre, 2015)	Inoculated with the GEN2.2 (BPDCN patient-derived cell line) $1x10^6$ cell/mouse n=8 mice in 3 independent experiments	2 µg/mouse tagraxofusp, IP, 5 daily doses for 1 cycle	Tagraxofusp significantly increases median overall survival, from 17 days in control mice to 58 ± 2 days in treated mice ($p<0.001$).
NSG Mouse (Christie, 2015)	BPDCN patient cells (CD45low CD123high HLA-DRhigh CD3-)	100 µg/kg tagraxofusp, IP, 5 daily doses for 2-3 cycles	Tagraxofusp reduces the number of human BPDCN cells in the peripheral blood, spleen, and bone marrow of mice implanted with human BPDCN cells. One cycle of tagraxofusp increases PFS (48 days in tagraxofusp-treated mice vs 12 days in vehicle-treated mice, $p<0.0001$). Tagraxofusp re-treatment upon relapse induces second and third peripheral blood remissions.
NSG Mouse (Mani, 2018)	AML patient cells	50 µg/kg tagraxofusp, IP, 3 times a week for 5 weeks	Tagraxofusp significantly increases overall survival of treated mice compared with those treated with the vehicle control ($p=0.0069$). Tagraxofusp reduces tumour burden in the bone marrow of treated mice.

Tagraxofusp treatment eliminated leukemic cells and extends survival in immunodeficient mice implanted with human BPDCN and AML cells (Angelot-Delettre, 2015; Christie, 2015; Mani, 2018).

Interspecies differences for IL-3 and CD123

A homology analysis of the amino acid sequence for IL-3 and CD123 from different species was conducted using the Basic Local Alignment Search Tool (BLAST) from the National Center for Biotechnology Information (Bethesda, MD).

Table 3 lists the amino acid sequence homology and identity between hIL-3, which is the targeting domain of tagraxofusp, and IL-3 from the indicated species.

Table 3: Homology and identity of the IL-3 amino acid sequence from the indicated species to hIL-3

Species	Homology to human IL-3	Identity to human IL-3
Cynomolgus monkey (Macaca fascicularis)	85%	81%
Mouse (Mus musculus)	50%	50%
Dog (Canis lupus familiaris)	52%	37%
Rat (Rattus norvegicus)	54%	30%
Rabbit (Oryctolagus cuniculus)	NA	NA

Abbreviations: BLAST = Basic Local Alignment Search Tool; IL-3 = interleukin-3; NA = not available.
Note: BLAST conducted on 10 January 2018 (Madden, 2002).

Table 4 lists the amino acid sequence homology and identity between CD123 from humans and the indicated species. Human IL-3 has been shown to bind to cynomolgus monkey IL-3R, and this species was previously chosen as the definitive toxicology model due to in vitro binding characteristics and because human IL-3 induces myeloid cells expressing cynomolgus IL-3R (Cohen, 2004; van Gils, 1994). IL-3 and CD123 from cynomolgus monkey and human have a much greater amino acid sequence homology and identity than any other species assessed, including rodent.

Table 4. Homology and identity of CD123 amino acid sequence from the indicated species to human CD123

Species	Homology to human CD-123	Identity to human CD-123
Cynomolgus monkey (Macaca fascicularis)	92%	87%
Rabbit (Oryctolagus cuniculus)	65%	49%
Dog (Canis lupus familiaris)	63%	44%
Rat (Rattus norvegicus)	46%	31%
Mouse (Mus musculus)	43%	30%

To confirm the species divergence of IL-3 and CD123 proteins, applicant conducted a non-GLP in vitro surface plasmon resonance-based binding assay to examine tagraxofusp binding to human and mouse CD123 (see in Table 4). For comparison and control, native IL-3 proteins from the respective species were also assessed. The findings indicated that tagraxofusp displays concentration-dependent, reproducible binding to the human CD123 and does not bind mouse CD123 under any of the testing conditions. The binding of tagraxofusp to rat, dog, and rabbit CD123 was not performed due to lack of commercially available reagents and because of the large divergence in sequence homology between human CD123 and these respective species. Previous studies have shown that human IL-3 can bind to cynomolgus monkey IL-3R and induce myeloid cells expressing cynomolgus IL-3R (Cohen, 2004; van Gils, 1994).

Secondary pharmacodynamic studies

No secondary PD studies were conducted by the applicant, the literature data has been submitted instead (see discussion on non-clinical aspects).

The table 5 below presents literature references on CD123 expression on normal cells.

Table 5. CD123 Expression on normal cells

Cell type	Study	Methods	Noteworthy findings
Plasmacytoid DCs	(Willmann, 2000) (Autissier, 2010)	Flow cytometry	Highly expressed on pDCs Higher expression on pDCs than myeloid DCs
Basophils	(Han, 2008)	Flow cytometry	Brightly expressed by basophils
	(Chen, 2009)	Flow cytometry, immunofluorescence	Highly expressed by peripheral blood and tonsillar basophils
	(Charles, 2012)	Flow cytometry	Highly expressed by basophils, similar levels as pDCs
Monocytes	(Elliott, 1989)	Radiolabelled binding assay	IL-3R is expressed on normal human monocytes
	(Sun, 1996)	Flow cytometry	Moderately expressed on freshly purified human monocytes
Eosinophils	(Sun, 1996)	Flow cytometry	Moderately expressed on freshly purified human eosinophils
	(Chen, 2009)	Flow cytometry, immunofluorescence	Expression on eosinophils is lower than expression on pDCs and basophils
Myeloid DCs	(Willmann, 2000)	Flow cytometry	Expressed at lower levels on myeloid DCs relative to pDCs
	(Sun, 2009) (Veckman, 2008)	Flow cytometry	Expressed at low to intermediate levels by CD11c+ myeloid DCs
Mast cells	(Gebhardt, 2002)	Flow cytometry, RT-PCR	Lowly expressed on intestinal mast cells but can be upregulated by SCF and IL-4
	(Dahl, 2004)	Flow cytometry	Lowly expressed on cord blood-derived, in vitro differentiated mast cells
Neutrophils	(Park, 1989)	Radiolabelled binding assay	Not expressed on primary human neutrophils
	(Smith, 1995)	Flow cytometry, RNAse protection assay, radiolabelled binding assay	Not expressed on freshly isolated human neutrophils but is upregulated by GM-CSF
Endothelial cells	(Korpelainen, 1995)	Flow cytometry, Northern blot	Lowly expressed on human umbilical vein endothelial cells but is upregulated by interferon gamma and TNF-α
	(Tettamanti, 2013)	Flow cytometry	Very lowly expressed on dermal and lung microvascular endothelial cells
	(Ceribelli, 2016)	Immunohistochemistry, immunofluorescence	Expressed on high endothelial venules of human tonsil
Osteoblasts	(Barhanpurkar, 2012)	RT-PCR, Western blot	Expressed on mesenchymal stem cells, pre-osteoblasts, and mature osteoblasts

Cell type	Study	Methods	Noteworthy findings
Hematopoietic progenitors	(Sato, 1993)	Flow cytometry	Lowly expressed on CD34+ hematopoietic progenitors
	(Munoz, 2001)	Flow cytometry	Lowly to moderately expressed on CD34+ CD33+ CD19- myeloid progenitors but not on CD34+ CD33- CD19+ CD10+ lymphoid progenitors
	(Manz, 2002)	Flow cytometry	Lowly expressed on CD34+ CD38+ common myeloid progenitor
	(Taussig, 2005)	Flow cytometry	Lowly expressed on CD34+ CD38- hematopoietic stem cells from bone marrow, lower expression level when compared with AML cells

Abbreviations: AML = acute myeloid leukaemia; DC = dendritic cells; GM-CSF = granulocyte macrophage colony-stimulating factor; IL = interleukin; IL-3R = interleukin-3 receptor; pDC = plasmacytoid dendritic cells; RT-PCR = reverse transcription polymerase chain reaction; SCF = stem cell factor; TNF-α = tumour necrosis factor alpha.

Additionally, it is stated in Urieto 2004 that binding of tagraxofusp to normal human tissues was evaluated in vitro by immunohistochemistry of frozen tissue sections fixed onto slides and no reactivity with tagraxofusp was observed in tissue from human BM, cerebellum, spinal cord, lung, heart, skeletal muscle, spleen, liver, pancreas, stomach, breast, adrenal gland, colon, kidney, urinary bladder, and skin, whereas detectable reactivity was observed with TF/H-ras cells that express high-affinity IL-3Rs.

Other malignancies than BPDCN that are known to express CD123 include myelodysplastic syndrome (MDS), certain myeloproliferative neoplasms, chronic myelogenous leukaemia (CML), both B- and T-cell acute lymphoblastic leukaemia, hairy cell leukaemia, Reed-Sternberg cells of Hodgkin disease, and certain aggressive non-Hodgkin lymphomas. CD123 is also expressed on the CSCs of AML, MDS, and CML. CD123 is also found on pDCs in the bone marrow microenvironment of certain malignancies including multiple myeloma (MM) and certain myeloproliferative neoplasms. A similar finding has been observed in chronic myelomonocytic leukaemia, where nodules of CD123+ pDCs were noted in the bone marrow as well as at extramedullary sites.

Safety pharmacology programme

Stand-alone studies to evaluate the potential effects of tagraxofusp on organ system function have not been conducted. As part of the MPI-2231-002 Good Laboratory Practice (GLP) repeat-dose toxicity study and the MPI-2231-007 GLP repeat-dose, multiple cycle toxicity study of tagraxofusp in cynomolgus monkeys, electrocardiogram examinations were conducted. In the 1-month study, ECGs were performed on all animals pre-test and at 1 to 2 hours post-dose on Days 1 and 4 and prior to recovery necropsy. There were no tagraxofusp-related effects on qualitative or quantitative ECG parameters at any time-point. The estimated tagraxofusp plasma concentrations at 2 hours post dose on Days 1 and 5 were 24 and 37 ng/mL at 30 µg/kg, and 44 and 141 ng/mL at 60 µg/kg. In the 3-month study, ECGs were performed on all animals pre-test and pre-dose on Days 29 and 56. There were no tagraxofusp-related effects on qualitative or quantitative ECG parameters at any time-point.

Pharmacodynamic drug interactions

No formal drug-drug interactions have been conducted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

No PK dedicated studies were performed. Evaluation of toxicokinetic parameters and anti-drug antibodies (ADAs) was performed in repeat-dose toxicity studies in cynomolgus monkeys and are presented below. In these studies, the blood samples were obtained in potassium EDTA anticoagulant tubes from a contralateral vein (sampling site was away from the site of administration). Samples were obtained as early as 1 minute after the completion of a slow 5-minute IV bolus dose.

Toxicokinetics were assessed after the first, second, and/or fifth doses and, in 1 study (pivotal toxicity/TK study), during three 28-day dosing cycles. In each study, a serial blood sampling plan was executed to collect samples for up to 4 hours after dosing to document exposure and characterise the distribution and elimination phases of tagraxofusp TK. Additional blood samples were collected to assess the presence of anti tagraxofusp reactive antibodies, also known as (ADA). The ADA assay results were used to screen the animals before selection for the nonclinical studies and for the detection of an immunological response to tagraxofusp during the study.

In addition, one PK "bioequivalence" study in cynomolgus monkeys has been performed as presented below.

Absorption

No absorption studies have been conducted with tagraxofusp. Tagraxofusp is administered by IV injection and absorption (systemic bioavailability) is 100% via this route.

As mentioned above the PK parameters were obtained mainly in the Studies MPI-2231-002; MPI-2231-007 (table 6).

Table 6: Toxicokinetic parameters collected in GLP toxicity studies 2231-002; 2231-007.

Study ID	Route duration	N	Dose µg/kg		$C_{t=0}$ ng/mL	$AUC_{0-\infty}$ µg·min/mL	$T_{1/2}$ min	CL ml/min/kg	Vz ml/kg
MPI Research Study 2231-002 **5-day repeat-dose toxicology study with 3-week recovery period** GLP	**IV injection QD × 5 consecutive days (5 doses)** TK Dose 1, Dose 5	Main Phase: 3/sex/dose level Recovery Period: 2/sex for the 0 and 60 µg/kg dose levels	30	D1	602	22.8	26.0	1.35	49.6
				D5	566	26.7	30.8	1.15	50.6
			60	D1	1170	44.8	25.7	1.37	50.1
				D5	1110	65.3	36.0	1.02	50.0
Study ID	**Route duration**	**N**	**Dose µg/kg**		**$C_{t=0}$ ng/mL**	**$AUC_{0-\infty}$ µg·min/mL**	**$T_{1/2}$ min**	**CL ml/min/kg**	**Vz ml/kg**
MPI Research Study 2231-007 **multiple-cycle toxicology study with 5-day dosing every month for 3 cycles** GLP	**IV injection QD × 5 consecutive days followed by 21 days off drug for 3 cycles (15 doses)** TK Cycle 1 (Days 1, 5) TK Cycle 2 (Day 27, 31) TK Cycle 3 (Day 54, 58)	3/sex/dose level	35	D1	543	327 **19.6**	0.474 **28.4**	2.02	82.3
				D5	309	281 **16.9**	0.504 **30.2**	2.33	102
				D27	252	158 **9.5**	0.563 **33.8**	6.06	310
				D31	16.4	28.9 **1.7**	0.606 **36.4**	20.2	1060
				D54	9.33	3.40 **0.2**	0.343 **20.6**	176	5110
				D58	ND	ND	ND	ND	ND
			45	D1	665	438 **26.3**	0.512 **30.7**	1.76	77.6
				D5	439	395 **23.7**	0.482 **28.9**	1.91	79.3
				D27	451	352 **21.1**	0.762 **45.7**	7.21	513
				D31	85.9	283 **17.0**	0.537 **32.2**	2.65	123
				D54	12.7	10.4 **0.6**	0.598 **35.9**	151	7100
				D58	ND	ND	ND	ND	ND

Distribution

No distribution studies have been conducted with tagraxofusp. The TK characteristics show that tagraxofusp has a relatively small volume of distribution (VZ). In repeat-dose GLP studies, the VZ following iv administration was between 50.1 ± 7.00 mL/kg (study 2231-002, data from first cycle) and up to 82.3±45.5 mL/kg (study 2231-007, data from first cycle). This volume is quite similar to the total blood volume (65 mL/kg) for the cynomolgus monkey, suggesting that tagraxofusp is not extensively distributed outside the systemic blood circulation compartment. In the 3-month study, the volume of distribution increased with treatment cycles.

Metabolism

No metabolism studies have been conducted with tagraxofusp.

Excretion

No excretion studies have been conducted with tagraxofusp. In repeat-dose GLP studies, tagraxofusp was rapidly cleared with a mean clearance ranging from 1.21 to 2.02 mL/min/kg. The terminal half-life was about 0.5 hours following iv administration.

Pharmacokinetic drug interactions

No in vitro or in vivo drug-drug interaction studies have been conducted.

Interspecies comparison

Monkey exposure to tagraxofusp has been demonstrated in TK studies to be dose-dependent and to decrease between cycles due to the development of ADAs. Notably in both monkeys and humans, concentrations of "free" tagraxofusp decrease over time with the continuing administration of the same tagraxofusp dose due to the development of reactive tagraxofusp antibodies (ADAs).

Table 7 presents the relative exposure multiple for systemic concentrations of tagraxofusp in animal studies compared with that achieved in the human clinical studies. The comparisons are based on Cmax and AUC exposure for the first cycle and first dose of 35 or 45 µg/kg in Study MPI-2231-007 (Cycle 1 Day 1) and for the overall exposure after the highest nonclinical dose (80 µg/kg) in non-GLP Study MPI-2231-001 to the Cmax and AUC exposure for the first cycle and first dose after doses of 7, 12, or 16 µg/kg in clinical Study STML-401-0114.

Table 7. Interspecies comparison (Cmax and AUC comparison)

Species	Study	N	Dose (µg/kg)	Cmax (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)
Human	STML-401-0114	6	7	29.1 ± 25.1	67.6 ± 16.3
		80	12	66.7 ± 66.7	142 ± 92.0
		6	16	76.3 ± 72.2	142 ± 115
Cynomolgus Monkey	MPI-2231-007	6	35	543 ± 125	327 ± 103
		6	45	665 ± 51.6	438 ± 74.0
	MPI-2231-001	4	80	1336 ± 126	3,240 ± 534

These comparative data showed that tagraxofusp Cmax exposure was at least 7 to 8.7 times higher during the nonclinical studies in monkeys when the monkeys were given a dose of 35 or 45 µg/kg compared with the tagraxofusp Cmax exposure after a 16 µg/kg dose in humans.

Tagraxofusp AUC exposure was at least 2.3 to 3 times higher in monkeys given a dose of 35 or 45 µg/kg compared with the tagraxofusp AUC exposure after a 16 µg/kg dose in humans. The dose of 80 µg/kg in cynomolgus monkeys produced a larger margin of exposure between the monkeys and humans.

Other pharmacokinetic studies

One non-GLP PK study of tagraxofusp in 8 female cynomolgus monkeys was conducted (MPI-2231-006). The objective was to assess the systemic exposure after iv administration of 2 formulations of tagraxofusp, frozen solution versus lyophilised formulation. On 2 separate study days 48 hours apart, a single tagraxofusp IV infusion (30 µg/kg) was administered using tagraxofusp prepared from either a frozen solution formulation or a lyophilised formulation. The administration sequence of lyophilised or frozen solution formulations was randomised according to a crossover design, and the C_{max} and AUC systemic exposure and disposition of tagraxofusp were compared using a non-compartmental analysis of tagraxofusp plasma concentrations measured by Eurofins Test Method GCL-279. The results are presented below.

Table 8. Exposure in cynomolgus monkey study MPI-2231-006

Toxicokinetic parameter (mean ± SD)	**Frozen solution (30 µg/kg)** Drug product lot no. ENG1509	**Lyophilised (30 µg/kg)** Drug product lot no. B150136
	Single dose (Crossover N=8)	**Single dose (Crossover N=8)**
C_{max} (ng/mL)	440 ± 99.9	465 ± 76.0
$AUC_{0-\infty}$ (ng·h/mL)	269 ± 74.7	285 ± 80.8
$AUC_{0-\infty}$ (µg·min/mL)	16.1 ± 4.48	17.1 ± 4.85

Note: $AUC_{0-\infty}$ units of (µg·min/mL) = (ng·h/mL) × 60/1000.

Tagraxofusp showed a small V_Z and a large CL. Across all animals and formulations, the mean (±SD) $t_{1/2}$ of the decline in tagraxofusp plasma concentration after the IV dose was 25.2±3.02 minutes (N=16). The mean (±SD) CL was 1.95±0.632 mL/min/kg and the mean (± SD) V_Z was 69.8±19.9 mL/kg (N=16).

2.3.4. Toxicology

Four repeat-dose toxicity studies were performed by the applicant in cynomolgus monkeys, two pivotal studies (one 1-cycle and one 3-cycle studies, GLP-claimed status) and two non-GLP were also submitted (1-cycle studies).

The two following toxicology studies were performed according to Good Laboratory Practices (GLP)-regulations:

- Study 2231-002: A 5-Day Intravenous Toxicity Study in Cynomolgus Monkeys with a 3-Week Recovery Period, completed on October 6, 2014, test facility: MPI Research, Inc. and EMD Millipore Corporation

- Study 2231-007: SL-401: A 3-month intravenous toxicity study in monkeys, completed on March 14, 2018, test facility: MPI Research, Inc. and Eurofins Pharma Bioanalytics Services US Inc.

Single dose toxicity

No single-dose toxicity studies were conducted with tagraxofusp (see discussion on non-clinical aspects).

Repeat dose toxicity

The toxicological profile of tagraxofusp was investigated in cynomolgus monkey.

Early non-GLP studies in cynomolgus monkeys were performed to support FIM clinical trial of tagraxofusp in an investigator-sponsored clinical study for the treatment of several haematologic malignancies, including BPDCN.

The published data are detailed below in table 9.

Table 9. Published early non-GLP studies with tagraxofup

Study no. GLP status	Number of animals	Dose levels Dose regimen	Major findings
Mice			
5-day efficacy study with survival data (Black, 2003)	20 All female	0, 2 µg (~100 µg/kg) IP injection QD for 5 days	Survival study; 5 QD injections of DT388IL3 induced a significant survival advantage over controls
Cynomolgus monkeys			
14-day toxicity Study (Cohen, 2004)	6 1/sex/group	40, 60, 100 µg/kg IV injection every other day (6 doses) **MTD:** 60 µg/kg for 6 doses administered every other day.	<u>Mortality:</u> <u>100 µg/kg :</u> 1F died Necropsy D6 or 7 moderate to severe vasculitis in multiple tissues (F) <u>Clinical observation/histopatho</u> <u>40 or 60 µg/kg</u> Necropsy D14 showed mild or moderate transient malaise and anorexia, respectively, without evidence of organ damage by blood tests or histopathology Bone marrow D14 (40) or D19 (60) : F myelosupp, M myeloid hyperplasia <u>100 µg/kg:</u> 1F died Necropsy D6 or 7 moderate to severe vasculitis in multiple tissues (F) showed severe malaise and anorexia Bone marrow D14: F myelosupp, M myeloid hyperplasia <u>ADA</u>: minimal 4 animals D12 days and 2 animals tested at D30 post treatment with anti-DT388IL3 levels < 1 mg/ml <u>TK</u> Dose 60 µg/ml : Conc à t30min= 0.45 µg/ml T1/2= 30 min with a peak concentration of 0.45 mg/ml or 10,000 pM

14-day toxicity Study (Cohen, 2005)	5 All female 2/dose group 1 control	0, 100, 150 µg/kg IV injection every other day (6 doses) **MTD not confirmed**	<u>100 µg/kg</u> moderate malaise and anorexia, but no consistent abnormalities in blood counts or serum chemistries regenerative myeloid hyperplasia and hepatic degeneration and regeneration (less severe than in 150 mg/kg group) <u>150 µg/kg</u> severe malaise and anorexia + moderate elevations of liver enzymes regenerative myeloid hyperplasia and hepatic degeneration and regeneration T1/2= 20 min with a peak concentration of approximately 2 µg/ml (30,000 pM) DT388IL3 can be tolerated at doses up to 100 µg/kg in a nonhuman primate, which is higher than previously reported dose-limiting toxicity (DLT) was vascular injury characterized by **vascular leak syndrome (VLS)** and fibrin deposition within blood vessels

Applicant's toxicology program was designed on the findings of these early non-GLP toxicity studies, 4 studies have been performed, as described below in table 10.

Table 10. Repeat-dose toxicity studies with tagraxofusp in cynomolgus monkeys

Study no. GLP status Date of protocol approved by sponsor	Duration Dose (µg/kg) Route	MTD/ HNSTD	Major findings
MPI-2231-001 **5-day Toxicity Study – Dose Range Finding** 1/sex/group GLP: **No** Age: 2 years and 4 months to 3 years and 5 months of age Experimental start and termination date: 23/10/13- 11/11/2013	**40, 60, 80** **IV bolus injection over a 5-min period** **QD** (5 total doses) No recovery Batch N° 184-TT1002A -P002-13 (B1 manufacturing process) <u>Vehicle:</u> **Phosphate Buffered Saline** (PBS) pH 7.4 <u>Stotrage conditions of SL401</u>: **Refrigerated** (2 to 8°C)	**MTD** 60 µg/kg/day (daily for 5 days) C(t=0)= 1100 ng/ml AUC0-∞= 47200 min.ng/mL	No histopathology performed, No actual dose received by the animals could not be confirmed. <u>Mortality</u> 1 M 80 euthanized in extremis D5 due to SL-401-related clinical signs: hunched posture, severely decreased activity, trouble gripping, decreased motor skills, limbs cold to touch, and no pain response in feet <u>Clinical observations</u> M+F all doses: dose dependent SL-401-related clinical signs of decreased activity, hunched posture, and hair sparse started prior D3 at 80, 4h after D4 at 60, D5 at 40 <u>Body weights</u> ↓ bw M 5-9% at 40, 60, 80 with an apparent inverse dose response relationship F 6% at 80 and 7% at 40 All 3F (40,60,80) + 1M(60 µg/kg/day): signs of inappetence <u>Hemato/coag, Clinical chemistry</u> LIVER M+F, ≥40 µg/kg, post D1: dose-dependent ↑ AST (up to 19.1x) and ALT (up to 9.3x) KIDNEY M+F, ≥40 µg/kg post D5: sporadic evidence of renal injury: ↑urea nitrogen (up to +2x) and/or creatinine (up to +2.9%) - mostly at 80 µg/kg/day: sporadic, inconsistent effects on neutrophils, platelet, and/or reticulocyte counts, - M+F ≥40 µg/kg: ↑ globulin (up to 30%) with ↓ albumin (up to 33%) and ↓ Ca <u>TK:</u> T1/2 around 0.5h C(t=0)= 629 ng/ml (40 µg/kg/day) to 1336 ng/mL (80 µg/kg/day) AUC0-∞= 23000 min.ng/mL (40 µg/kg/day) to 54000 min.ng/mL (at 80 40 µg/kg/day) <u>ADA</u> : 3/6

MPI-2231-004 **5-day Toxicity Study** 1/sex/group GLP: **No** Initial Age: 2 years and 9 months - 4 years and 11 months Experimental start and termination date: 30/12/2013-06/01/2014 SL-401 in a new vehicle formulation (5% Dextrose in water USP), in Cynomolgus monkeys to aid in dose selection for inclusion in the definitive toxicology assessment of SL-401.	**30, 60** **IV bolus injection over a 5-min period** **QD** **(5 total doses)** No recovery Batch N°184-TT1002-P001-13 (B1 manufacturing process) Vehicle **5% Dextrose** for Injection, USP Stotrage conditions of SL401: **Refrigerated** (2 to 8°C)	60 µg/kg: well tolerated No TK analysis	No histopathology performed, No actual dose received by the animals could not be confirmed, no TK/ADA analysis Mortality no death Clinical observations: no signs of inappetence INJECTION SITE 60 µg/kg: M swelling D1-5 + redness D1,5, F redness D2,3 30 µg/kg: F swelling D3 + redness D1-5, M redness D2-4 Body weights: ↓ dose dependent SL-401-related body weight: 60 µg/kg M+F 8%, 30 µg/kg/day M 7% F 4% Hematology and Clinical Chemistry - M+F, 30 +60, evidence of an INFLAMMATORY RESPONSE, mild to moderate ↑ neutrophils (up to +3.1-fold) and/or alterations in serum proteins: ↓ erythrocytes, hemoglobin and haematocrit (up to -23%), Albumin (up to -14%) and a mild ↑ platelets (+35%), globulin (up to +38%), - M 30 and M+F 60, ↓ reticulocytes (up to -78%) - M+F, 30+60, ↑ AST (up to +4.2x) and ALT (up to +5.3x) - No alteration in urea nitrogen

MPI-2231-002 **5-day Toxicity Study with 3 week recovery** Terminal: 3/sex/group Recovery(CRTL+HD) : 2/sex/dose Group GLP: **Yes** Age: 2 years and 7 months to 3 years and 8 months of age Pre-screened negative for the presence of pre-existing anti-diphtheria antibodies Experimental start and termination date: 09/01/2014-05/02/2014	0, 30, 60 **IV bolus injection over a 5-min period** **QD** **(5 total doses)** **3-week Recovery** Batch N°184-TT1002-P001-13 (B1 manufacturing process) Vehicle (admendment3) **5% Dextrose** for Injection, USP Stotrage conditions of SL401: **Refrigerated** (2 to 8°C)	**HNSTD 30 µg/kg/day** Cmax D1: 602 ng/mL D5: 566 ng/mL overall AUC D1: 22.8 min.µg/mL D5: 26.7 min.µg/mL	GLP issues see GLP section in this report Mortality 1F 60, D6 euthanasia, cause of death: severe necrosis of renal cortical tubules Clinical observations INAPPETENCE D2 2F 60, D4 and 5 all animals, *persisted at recovery at 60*, treated by administration supplemental fluids INJECTION SITE scabbing and/or red discoloration all animals treated+CRTL, *recovery delayed at 60* Body weight D1-D5 : ↓ M 30 (-3%), M 60 (-6%), F 30 and 60 (-6%), ↓ *until -7% in recovery phase correlated with inappetance* Ophthalmoscopic and electrocardiographic examinations None Hematology, coagulation, clinical chemistry, and urinalysis endpoints KIDNEY ↑ urea nitrogen (up to +2.1x) (*remained increased at rec*) and creatinine M+F 60 (up to +2.3x), ↑ proteinuria F30, M+F60 (dose dpdt in F *partly reversible*, ↓ urine volume (-86%) *reversible* and ↓ albumin, correlated with tubular necrosis and degeneration ERYTROPOEISIS ↓reticulocytes M+F 30 and 60 (D3 up to-80%) partly reversible up to-18% at 60) consistent with sup. erythropoiesis LIVER 2M+3F 30, M+F 60: ↑ AST (+19.1x and ALT (+7.8x), *mostly reversible* INFLAMATORY RESPONSE all animals: ↑ neutrophils (up to 2.6x) dose dpdt in F, *reversible*, presence of Döhle bodies, ↑ fibrinogen and globulin (dose dpdt up to+30%)(*reversible*), ↓ albumin dose dpdt (up to -30%) *partly reversible*, ↓ Ca (ip to -16%) *reversible* LYMPHOID DEPLETION all animals: ↓ lymphocytes (up to 40%) dose dpdt in M and other leukocyte subtypes (*reversible):* monocytes (up to -52%), eosinophils (up to -91%) and basophils (up to -63%) BLOOD COAGULABILITY all animals: ↑ APTT (up to +63%; +up to 13.0 sec) and prothrombin time (up to +15%;+up to 1.8 sec) INAPPETENCE CSQ All animals: ↓ phosphorus (up to -43%) (*not reversible*), all M 60 ↑ triglycerides (up to +6x) (*reversible*), volume (*reversible*) and increases in specific gravity Anatomic pathology: macro and microscopic changes **KIDNEY** M60 ↑ kidney weight, 1M 60 tan discoloration in kidneys, + microscopic tubular necrosis/degeneration F30 and M+F 60, 1 M at 60 ↑ hyaline droplets within tubular epithelium, *no finding at recovery time necropsy* **THYMUS** 1 M60 at recovery: small thymus + microscopic generalized lymphoid depletion (all animal except M30), *partly reversible* **LIVER**

			M 60: ↑ liver weight + minimal centrilobular hepatocellular necrosis and mild vacuolation (centrilobular or diffuse), *no finding at recovery time necropsy*
			BRAIN inflammation/necrosis/degeneration of the choroid plexus M+F 30 and 60 (*not reversible*) 1 F 60 :minimal haemorrhage necrosis/degeneration in areas of epithelial cells lining with free leukocytes and cellular debris within brain ventricles (1M 30 and 1F 60) (*recovery: ↓ leukocytes but there was an increased presence of fibrous stroma, epithelial cells lining the choroid plexus were focally attenuated or appeared disorganized*)
			ADA D14 and 28: 3/3 remaining (1 died): all positive, but only 3 animal tested TK (see below PK part of this report)
MPI-2231-007 **3 cycles of 5-day Toxicity Study** 3/sex/group GLP Experimental start and termination date: 27/04/2017-03/07/2017 Age: 2 years and 5 months to 4 years and 1 months of age	**0, 35, 45** **IV bolus injection over a 5-min period** **3 cycles of 5 consecutive QD doses, separated by 21-day or 22-day periods without dosing** No recovery Batch N°184-TT1002A-P002-13 (B1 manufacturing process) Vehicle **0.9% Sodium Chloride** for Injection, USP Stotrage conditions of SL401: **frozen** (-60 to -90°C)	No NOAEL Target organs confirmed : choroid plexus, kidney, liver, thymus, blood manifestation	Mortality 1 F 45 D9 euthanasia, moderate decreased activity, thin, moderate dehydration, increased body temperature, bruising of the abdomen and hind limbs, and swelling of the right inguinal area, hind limbs, and dosing site cause of death: **not determined,** microscopic changes to the choroid plexus of the brain similar to other test article-treated animals, although the mononuclear cell infiltrate/inflammation was more severe comparatively (moderate) and necrotic cell debris and free leukocytes were present within the ventricular lumen Clinical observations ≥35 µg/kg/day in M+F; hunched posture, thin, dry skin ≥35 µg/kg/day in F; decreased activity, inappetence, tremors, hunched posture, thin, dry skin Body weight ↓ M 35 (D6->22 and 26->34) -6.4% to -10.8%, 45 (D6-22 and D26->38) -8.7% to -13.3% Start by D64, ↑ M+0.5% at 35 µg/kg -5.1% for the 45 µg/kg males. Ophthalmoscopic and electrocardiographic examinations None

Clinical chemistry

Dose level	Day	35		45	
		M	F	M	F
Globulin[a]	7	+15%	+16%	+22%	+8%
	34	+23%	+34%	+28%	+32%
	68	+9%	+12%	+18%	+7%
Albumin[a]	7	-20%	-18%	-21%	-29%
	34	-12%	-9%	-21%	-13%
	68	-	-	-	-
Phopsphorus[a]	7	-21%	-	-32%	-49%
	34	-	-	-19%	-20%
	68	-	-	-	-
AST[a]	7	+44%	+59%	+125%	+185%
	34	-	-	+46%	-
	68	-	-	-	-
ALT[a]	7	+44%	+138%	+137%	+162%
	34	-	-	+107%	-
	68	-	-	-	-

[a]Percent change relative to pre-test.

Hematology/Coagulation

Dose level	Day	35		45	
		M	F	M	F
Hemoglobin[a]	7	-	-12%	-	-12%
	34	-11%	-10%	-12%	-6%
	68	-	-	-6%	-6%
Reticulocytes[a]	7	-64%	-56%	-70%	-85%
	34	-35%	-24%	-60%	-70%
	68	-	-	-	-56%
Platelets[b]	7	-	-	-	-21%
	34	-	-	-	-
	68	-	-	-	-
Fibrinogen[a]	7	+96%	+103%	+97%	+117%
	34	+33%	+32%	+32%	+47%
	68	-	-	-	-
APTT[a]	7	+18%	+17%	+25%	+21%
	34	-	-	-	-
	68	-	-	-	-

[a]Percent change relative to control mean
[b]Percent change relative to pretest

Urinalysis:
no remarkable findings

Anatomic pathology: macro and microscopic changes

Dose level (µg/kg)	0		35		45	
	M	**F**	**M**	**F**	**M**	**F**
No of animals	3	3	3	3	3	3
Brain, choroid plexus						
Degeneration /necrosis/	0	0	2	2	3	3
Minimal	0	0	0	2	1	1
Mild	0	0	1	0	0	2
Moderate	0	0	1	0	2	0
Infiltration/inflammation/mononuclear cell	0	0	2	2	2	3
Minimal	0	0	2	2	2	1
Mild	0	0	0	0	0	1
Moderate	0	0	0	0	0	1
Fibrosis	0	0	2	0	2	1
Minimal	0	0	2	0	1	1
Mild	0	0	0	0	1	0
Pigment	0	0	2	0	1	1
Minimal	0	0	1	0	1	1
Mild	0	0	1	0	0	0
Adhesion	0	0	1	0	1	0
Minimal	0	0	1	0	1	0
Thymus						
Depletion, lymphoid, generalised	0	0	0	2	2	2
Minimal	0	0	0	1	1	0
Mild	0	0	0	1	1	1
Moderate	0	0	0	0	0	1

ADA:
68 samples tested: 24/68 in control animals: no ADA tested + 44/68 in treated animals: ADA observed in 5/12 treated animals as follow 4/7 at 35 µg/kg 3/7 at 45 µg/kg

TK (see below PK part of this report)

The GLP repeat-dose studies have identified kidney, liver, thymus, brain choroid plexus and blood manifestations as the main tagraxofusp-related toxicities. All toxicities with exception of decreased body weight and the findings in thymus and choroid plexus showed recovery following ceased dosing. Overall, the toxicities seemed less pronounced in the 3-month study.

Genotoxicity

Studies to address genotoxic potential have not been conducted (see discussion on non-clinical aspects).

Carcinogenicity

Studies to address carcinogenic potential have not been conducted (see discussion on non-clinical aspects).

Reproduction Toxicity

The fertility, early embryonic development, and pre- and postnatal toxicology studies have not been performed. A literature-based assessment on the potential adverse effects of tagraxofusp on embryo-foetal development was provided. It focused on the potential adverse effects of targeting the IL3 pathway in reproduction and development. The provided data suggest potential effects on foetal haematopoiesis through exposure to exogenous IL3 or blockade of IL3 signalling (data not shown).

Toxicokinetic data

Monkey (5 days IV administration at 40, 60, and 80 µg/kg/day, MPI-2231-001, non-GLP)

There were no appreciable differences in the TK profile between male and female animals or between the first and fifth doses of tagraxofusp. The mean elimination $t_{1/2}$ was 28.8 ± 4.0 minutes across all doses and all animals; mean plasma clearance (CL) was 1.52 ± 0.28 mL/min/kg and the mean volume of distribution (V_Z) was 62.2±8.8 mL/kg. The maximum plasma concentration values estimated as $C_{t=0}$, the back extrapolated concentrations calculated to occur at the end of the 5-minute infusion, were 629±64, 1100±213, and 1336±126 ng/mL (N=4 per dose level for 2 animals after both the first and fifth doses) for the 40, 60, and 80 µg/kg doses, respectively. Similarly, the $AUC_{0-\infty}$ values were 23.0±2.9, 47.2±7.2, and 54.0±8.9 µg·min/mL at 40, 60, and 80 µg/kg/day, respectively.

Table 11. Toxicokinetic parameters averaged for the first and fifth doses in in cynomolgus monkeys in study MPI-2231-001

	Toxicokinetic exposure parameter (mean ± SD)				
Dose (µg/kg)	**$t_{1/2}$ (min)**	**$C_{t=0}$ (ng/mL)**	**$AUC_{0-\infty}$ µg·min/mL**	**V_Z (mL/kg)**	**CL (mL/min/kg)**
40 (N=2)	25.6 ± 3.6	629 ± 64.1	23.0 ± 2.9	64.8 ± 8.9	1.76 ± 0.20
60 (N=2)	32.2 ± 4.6	1100 ± 213	47.2 ± 7.2	59.9 ± 8.0	1.29 ± 0.31
80 (N=2)	28.5 ± 1.4	1336 ± 126	54.0 ± 8.9	61.9 ± 7.8	1.51 ± 0.26

Animals were sampled for ADA analysis (Eurofins Test Method GCL-320) prior to dosing. Three of 6 animals were classified as being negative and the other 3 animals were confirmed as positive for presence of reactive antibodies. However, the positive samples displayed minimal titres (1:8); the assay minimal required dilution.

Monkey (1 cycle of 5 days IV administration at 30 and 60 µg/kg/day followed by ~ 21 days recovery, MPI-2231-002, GLP)

There were no substantial differences in the TK profile between male and female animals, but there were slight differences (a lower CL and longer $t_{1/2}$) between the fifth versus first doses. The mean CL across both doses and animals was 1.21±0.304 mL/min/kg, the mean V_Z was 50.1±7.0 mL/kg, and the mean elimination $t_{1/2}$ was 29.9±6.72 minutes. The elimination $t_{1/2}$ of tagraxofusp is short relative to the interval between consecutive QD doses. Therefore, there was no accumulation of the drug. The tagraxofusp plasma concentrations at the end of dose administration, $C_{t=0}$, were similar for the first and fifth doses. There was a small increase in the $t_{1/2}$ of tagraxofusp corresponding to a small decrease in CL of tagraxofusp and reflected in an increase in the AUC between the fifth versus the first dose. This change is noted in the means and was observed in almost all individual animals.

Table 12. Toxicokinetic parameters in cynomolgus monkeys in study MPI-2231-002

	30 µg/kg/day		60 µg/kg/day	
Toxicokinetic parameter (mean ± SD)	**Day 1 (1st dose)**	**Day 5 (5th dose)**	**Day 1 (1st dose)**	**Day 5 (5th dose)**
$C_{t=0}$ (ng/mL)	731 ± 89.1	637 ± 65.6	1370 ± 138	1230 ± 180
C_{max} (ng/mL)	602 ± 67.4	566 ± 61.7	1170 ± 115	1110 ± 159
$AUC_{0-\infty}$ (µg·min/mL)	22.8 ± 4.26	26.7 ± 4.77	44.8 ± 6.60	65.3 ± 22.9
V_Z (mL/kg)	49.6 ± 6.02	50.6 ± 7.15	50.1 ± 5.79	50.0 ± 9.29
CL (mL/min/kg)	1.35 ± 0.259	1.15 ± 0.198	1.37 ± 0.242	1.02 ± 0.339
$t_{1/2}$ (min)	26.0 ± 4.44	30.8 ± 3.20	25.7 ± 1.90	36.0 ± 7.93

Note: $AUC_{0-\infty}$ units of (µg·min/mL) = (ng·min/mL) / 1000.

Animals were sampled for ADA analysis (Eurofins Test Method GCL-320) prior to dosing and on Days 14 and 28 (i.e. during the recovery phase). No pre-existing ADAs were detected at randomisation and all control animals remained negative for ADAs throughout the study. Samples from animals given tagraxofusp at 60 µg/kg were all (n=3) reported as ADA-positive at Days 14 and 28. As shown in Table 14 Tier 2b inhibition by excess DT ranged from 7.7% to 94.2%, and Tier 2b inhibition by excess hIL-3 ranged from 1.3% to 75.9%. Tier 3 titres ranged from 1/32 to 1/1024. Based on these ADA Tier 2b results for domain specificity, monkey #219 predominantly had an antibody response against the DT domain, monkey #221 predominantly had an antibody response against the hIL-3 domain, and monkey #226 displayed antibodies against both DT and hIL-3 domains of tagraxofusp.

Table 13. Summary of samples positive for ADAs in cynomolgus monkeys in study 2231-002

Animal	Sex	Interval	ADA testing results and ADA titre				
			Tier 1	Tier 2a	Tier 3	Tier 2b	
						% inhibition	
			Result	Result	Titre	DT	hIL-3
226[a]	F	Pre-study	Not detected	Not determined	ND	ND	ND
		Day 14	Detected	Confirmed	1/1024	13.4	1.3[b]
		Recovery	Detected	Confirmed	1/512	23.5	42.9
219	M	Pre-study	Not detected	Not determined	ND	ND	ND
		Day 14	Detected	Confirmed	1/64	94.2	14.4[b]
		Recovery	Detected	Confirmed	1/32	85.4	11.8[b]
221	M	Pre-study	Not detected	Not determined	ND	ND	ND
		Day 14	Detected	Confirmed	1/256	15.3[b]	33.3
		Recovery	Detected	Confirmed	1/1024	7.7[b]	75.9

[a] One female in Group 3 was euthanised in extremis on Day 9 based on declining clinical condition.
[b] The % inhibition was not above the cut-point.

Monkey (3 cycles of 5 days IV administration at 35 and 45 µg/kg/day followed by ~ 21 days recovery, MPI-2231-007, GLP)

Tagraxofusp plasma concentrations declined mono-exponentially after administration as a 5-minute IV infusion to each animal. Even though the doses were administered based upon the individual animal's body weight, the exposure in the male cynomolgus monkeys was higher than the exposure for the female animals. Average exposure in female animals based upon the female:male AUC ratio was about 62% to 92% of the exposure observed in male animals. Higher concentrations in male animals were consistently observed throughout the study although inter-animal variability in the exposure was large (coefficient of variation ranging from 7.7% to 78.5%). The large variability among all animals suggested that tagraxofusp plasma concentration exposure was likely not statistically or meaningfully different.

Average tagraxofusp plasma concentration exposure was higher for the 45 µg/kg dose compared with that for the 35 µg/kg dose. Higher plasma concentration exposure in the 45 µg/kg dose group persisted throughout the study. However, regardless of dose, plasma concentration exposure decreased between cycles, with the second and third cycles demonstrating progressively lower exposure. The $t_{1/2}$ of tagraxofusp did not change remarkably between the cycles, being consistently about 0.5 hours in most cases, whereas both CL and the V_Z appeared to increase. The notable decrease in tagraxofusp plasma concentration exposure as the cycles progressed is attributed to a time-dependent increase in the development of ADAs. From the tagraxofusp C_{max} and AUC exposure data, it appears that there was an immunogenic response to the administration of tagraxofusp that increased over time, resulting in lower systemic C_{max} and AUC exposure in the animals in the second and third cycles. Each dosing cycle had progressively lower systemic exposure to the point that by cycle 3, on Day 58, the number of data points with measurable tagraxofusp concentrations did not permit the assessment of PK parameters.

The ELISA assay (Test Method GCL-279) of tagraxofusp in monkey plasma was designed for quantification of "free" (ie, not antibody-bound) tagraxofusp in plasma. The observed decrease in tagraxofusp exposure in the second and third cycles, therefore, only relates to unbound, i.e., "free," tagraxofusp. While not measured, it is possible that ADA-bound tagraxofusp may persist longer and possibly may reflect the rate of turnover of the antibodies. The increase in ADAs did not appear to

impact the $t_{1/2}$ of tagraxofusp in monkeys, suggesting that the ADAs did not impact the elimination process of unbound tagraxofusp.

There was a substantial increase in both the CL and the V_Z of tagraxofusp. The consistent elimination $t_{1/2}$ of the free tagraxofusp plasma concentrations suggests that the ratio of CL/V_Z remained relatively constant across the 3 cycles of dosing. The changes in PK parameters and exposure of tagraxofusp over time suggest that the formation of ADAs likely interfered with the measurement of free tagraxofusp in plasma due to ADA binding.

Table 14. Toxicokinetic parameters in cynomolgus monkeys given 5 daily doses of 35 µg/kg tagraxofusp for 3 cycles in study MPI-2231-007

Cycle/ Day	Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_z (mL/kg)
1/ 1	N	6	6	6	6	6	6	6
	Mean	543	NC	326	327	0.474	2.02	82.3
	Median	528	0.17	344	345	0.463	1.70	67.9
	CV%	23.1	NC	31.6	31.5	11.3	46.6	45.5
1/ 5	N	6	6	6	6	6	6	6
	Mean	309	NC	275	281	0.504	2.33	102
	Median	329	0.58	314	322	0.510	1.82	81.5
	CV%	23.7	NC	31.3	31.4	3.23	42.6	43.4
2/ 27	N	6	6	6	6	6	6	6
	Mean	252	NC	154	158	0.563	6.06	310
	Median	204	0.17	104	106	0.607	5.57	169
	CV%	72.2	NC	78.6	79.1	32.3	66.3	87.9
2/ 31	N	2	2	2	2	2	2	2
	Mean	16.4	NC	18.3	28.9	0.606	20.2	1060
	Median	16.4	0.58	18.3	28.9	0.606	20.2	1060
	CV%	NC	NC	NC	NC	NC	NC	NC
3/ 54	N	3	3	3	3	3	3	3
	Mean	9.33	NC	3.47	3.40	0.343	176	5110
	Median	6.58	0.17	3.29	3.40	0.343	176	5110
	CV%	66.1	NC	34.5	NC	NC	NC	NC

Note: Pharmacokinetic parameters on Study Day 58 are not summarised because the tagraxofusp plasma concentration time data were insufficient to permit calculations.

Table 15. Toxicokinetic parameters in cynomolgus monkeys given 5 daily doses of 45 µg/kg tagraxofusp for 3 cycles in study MPI-2231-007

Cycle/ Day	Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_z (mL/kg)
1/ 1	N	6	6	6	6	6	6	6
	Mean	665	NC	436	438	0.512	1.76	77.6
	Median	666	0.17	459	460	0.521	1.63	74.0
	CV%	7.76	NC	16.9	16.9	6.33	17.9	17.5
1/ 5	N	6	6	6	6	6	6	6
	Mean	439	NC	386	395	0.482	1.91	79.3
	Median	434	0.58	381	390	0.501	1.93	80.5
	CV%	5.91	NC	8.04	8.58	9.98	8.14	7.42
2/ 27	N	4	4	4	4	4	4	4
	Mean	451	NC	347	352	0.762	7.21	513
	Median	431	0.17	323	330	0.831	5.29	380
	CV%	97.8	NC	96.7	96.2	20.0	106	109
2/ 31	N	3	3	3	3	3	3	3
	Mean	85.9	NC	96.9	283	0.537	2.65	123
	Median	12.6	0.58	11.2	283	0.537	2.65	123
	CV%	157	NC	160	NC	NC	NC	NC
3/ 54	N	4	4	4	4	4	4	4
	Mean	12.7	NC	9.34	10.4	0.598	151	7100
	Median	7.06	0.17	4.71	5.62	0.568	137	6140
	CV%	109	NC	123	113	23.2	76.3	73.4

Note: Pharmacokinetic parameters on Study Day 58 are not summarised because the tagraxofusp plasma concentration time data were insufficient to permit calculations.

Samples for ADA analysis were obtained before dosing and on Days 14, 26, 53, and 68 and assessed by Eurofins Test Method GCL-320.

It should be noted that Test Method GCL-320 possesses an unusually high confirmatory cut point (80% inhibition); confirmatory cut points are typically in the 15% to 30% inhibition range. Before performing the cut point analysis, a scientific review of the assay signals and percent inhibition values for 51 normal monkey serum samples was performed by scientists representing the sponsor and the statisticians performing the statistical analyses. After the review, 36 of the 51 samples were considered to be antibody-positive and the remaining 15 samples were classified as antibody-negative. The observed high rate of pre-existing antibodies in the monkey population is not unexpected due to exposure to DT and subsequent conversion to antibody-positive. The 15 antibody-negative samples were used in this cut point analysis. For Study MPI-2231-007, the vehicle-treated monkeys all had baseline responses around 100 relative light units, which suggests a very low level of pre-existing ADAs. Thus, this finding suggests the originally computed confirmatory cut point (80% inhibition) may not be appropriate for this group of animals.

The monkeys in the 2 groups treated with either 35 or 45 µg/kg/day exhibited an increase in ADAs that was notable by Study Day 14. High ADA response in the Tier 1 assay continued throughout the study in the treated animals. Monkeys in the control group exhibited no detectable ADAs throughout the study.

ADAs were detected in 5 of 12 animals that received tagraxofusp at any point in the study (Table 15). Titres ranged from 1:2048 to 1:256. Four of the 7 positive ADA samples were observed at the 35 µg/kg dose level, while the remaining 3 positive samples were observed at the 45 µg/kg dose level. Titres were typically similar between the 35 and 45 µg/kg dose levels. Six of the 7 samples that were positive for ADAs occurred in males. Only 2 animals (Animals 2003 and 3003) on the study had detectable ADAs at more than 1 timepoint (Day 14 and Day 26) and both animals were male. When detected, ADAs were typically observed on Day 14 or 26. Antidrug antibodies in 1 animal were detected on Day 53 (Animal 3002; 45 µg/kg dose level male). The presence of ADAs was not detectable in any samples on Day 68.

Table 16. Summary of samples positive for ADAs in cynomolgus monkeys in study MPI-2231-007

Animal	Dose level	Sex	Positive sample	Tier2b (% inhibition)	
				DT	hIL-3
2001	35 µg/kg/day	Male	Day 26	55.7 (Day 26)	26.5 (Day 26)
2003	35 µg/kg/day	Male	Days 14 and 26	Assay failed (Day 14) and 25.3 (Day 26)	39.7 (Day 14) and 19.8 (Day 26)
2503	35 µg/kg/day	Female	Day 14	Assay failed (Day 14)	37.4 (Day 14)
3002	45 µg/kg/day	Male	Day 53	32.8 (Day 53)	0.6 (Day 53)
3003	45 µg/kg/day	Male	Days 14 and 26	0 (Day 14) and 50.3 (Day 26)	5.9 (Day 14) and 8.5 (Day 26)

The proposed clinical dose for marketing approval is 12 µg/kg for 5 consecutive days every 21 days. In humans, a dose of 12 µg/kg tagraxofusp produced a C_{max} of 66.7±66.7 ng/mL and an $AUC_{0-\infty}$ of 142±92.0 ng·h/mL on cycle 1 Day 1 (N=80 patients).

Human exposure (C_{max} and AUC) to tagraxofusp has been demonstrated in clinical studies to be dose-dependent and to decrease by cycle 3 due to the development of ADAs. Similarly, monkey exposure to tagraxofusp has been demonstrated in TK studies to be dose-dependent and to decrease between cycles due to the development of ADAs. Therefore, the aspects of dose-dependent exposure and time-dependent ADA effects make the comparative exposure in monkeys and humans more complicated. Table 17 shows the relative exposure multiple for systemic concentrations of tagraxofusp in animal studies compared with that achieved in the human clinical studies. The comparisons are based on C_{max} and AUC exposure for the Day 1 exposure in the 1- and 3-month studies to the C_{max} and AUC exposure for the first cycle and first dose after doses of 7, 12, or 16 µg/kg in clinical study STML-401-0114.

Table 17. C_{max} and AUC exposure in cynomolgus monkeys (studies MPI-2231-002 and MPI-2231-007, cycle 1 Day 1) compared with that in humans (study STML-401-0114, cycle 1 Day 1)

Species	Study	N	Dose (µg/kg)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Human	STML-401-0114	6	7	29.1 ± 25.1	67.6 ± 16.3
		80	12	66.7 ± 66.7	142 ± 92.0
		6	16	76.3 ± 72.2	142 ± 115
Cynomolgus Monkey	MPI-2231-002 (1-month study)	6	30	602 ± 67.4	380 ± 71
		10	60	1170 ± 115	747 ± 110
Cynomolgus Monkey	MPI-2231-007 (3-month study)	6	35	543 ± 125	327 ± 103
		6	45	665 ± 51.6	438 ± 74.0

Note: Units for C_{max} and $AUC_{0-\infty}$ were transformed into the same units for all species for the comparisons represented in this table.

Local Tolerance

Local tolerance was assessed in toxicity studies. Minimal to mild perivascular haemorrhage/necrosis were observed at the injection site.

Other toxicity studies

None

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has submitted a justification for omitting an environmental risk assessment studies stating that tagraxofusp being a fusion protein is expected to be removed by the following common pathways: degradation by proteolysis, nonspecific endocytosis, or target-mediated clearance, and further metabolized into component peptides and amino acids. As a consequence, metabolism studies have not been performed.

In view of the fact that tagraxofusp is a protein, the expected metabolism, the rarity of the indicated condition and taking into account the drug product excipients (tromethamine, sodium chloride, sorbitol (E420), water for injections), environmental risk assessment studies are considered not to be required, and the environmental risk is considered to be negligible.

2.3.6. Discussion on non-clinical aspects

The nonclinical safety profile of tagraxofusp has been characterized *in vitro* and *in vivo* pharmacological, pharmacokinetic and toxicological studies in mice and in monkeys. This nonclinical development program was designed in accordance with ICH S9 and ICHS6 guidelines, regarding the treatment of patients with advanced cancer and is sufficient to support marketing authorization of tagraxofusp in BPDCN patients.

The pharmacological profile of tagraxofusp was demonstrated in *in vitro* assays and in *in vivo* BPDCN model xenografted in rodents. The proof of concept was demonstrated, including apoptosis of BPDCN by tagraxofusp and increase in overall survival in xenografted mice. No studies have been submitted to validate the species selection and to characterize the binding affinity in monkey compared to human and consequently to determine the relevance of the species to clinical pharmacological activity and toxicology Given however the complete lack of binding observed between tagraxofusp and mouse CD123 together

with the low amino acid sequence homology between CD123 from humans versus CD123 from mouse, rat, dog, and rabbit it is unlikely that tagraxofusp binds to CD123 from these species. Taken together, these data showed that the cynomolgus monkey is the only pharmacodynamically relevant species for nonclinical toxicology testing.

No secondary PD studies were conducted by the applicant. Instead a literature review has been presented. In normal tissue, CD123 expression is limited and includes high expression on pDCs and basophils; moderate to low expression on monocytes, myeloid dendritic cells, eosinophils, and mast cells; and low to absent expression on haematopoietic stem cells

PK profile of tagraxofusp has been evaluated in repeated-dose toxicity studies after intravenous administration for 5 consecutive days per cycle in from one- to three-cycles treatment regimen in monkeys. Globally tagraxofusp shows approximate dose proportional exposure and no appreciable differences in the TK profile between male and female. CL and Vz appeared to increase after repeated cycles. Exposure decreased dramatically after the second cycle and almost no exposure was observed in the third cycle due to presence of ADA.

No formal drug-drug interactions have been conducted. Given the highly selective binding affinity between human IL-3 and human IL-3R, pharmacodynamic drug interactions would not be expected for any concomitant medication.

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, 3 weeks after dosing stopped. It is unknown if these findings are CD123 receptor-mediated or non-receptor mediated effects since binding of tagraxofusp to cynomolgus monkey CD123 has not been demonstrated. These findings in kidney and choroid plexus are considered likely relevant for the clinical situation.

The CHMP and PRAC requested additional pharmacovigilance activity in the RMP: Immunohistochemistry staining of brain tissue samples from non-clinical Study MPI 2231 007 to address the Important potential risk of 'Choroid plexus lesions' (however, the issues identified in the application prevent recommending granting a marketing authorisation).

Moreover, it seems likely that study animals had no existing anti-tagraxofusp antibodies at start of administration. As the histopathological findings observed in the choroid plexus, liver, and kidney were seen after only five consecutive dose administrations, involvement of ADAs/immuncomplexes seem unlikely. The toxicities observed in these organs could be driven by target binding-mediated effects, DT-mediated effects, or some combination of the above. However, immunocomplexes may potentially be involved in exacerbation of the findings.

No genotoxicity or carcinogenicity studies were conducted in accordance with ICH S6 guideline, it is endorsed. Tagraxofusp is a recombinant protein and is therefore not expected to interact directly with DNA.

Further non-clinical reprotoxicity studies are not warranted. 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. The effects of diphtheria toxin exposure on placental and embryo-foetal development are unknown. Elzonris should not be used during pregnancy unless the clinical condition of the woman requires treatment with tagraxofusp. It is unknown whether tagraxofusp/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

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

The CHMP agreed with the applicant that tagraxofusp being a fusion protein is expected to be removed by the common pathways: degradation by proteolysis, nonspecific endocytosis, or target-mediated clearance, and further metabolized into component peptides and amino acids. Furthermore, in light of the rarity of the indicated condition and taking into account the drug product excipients tagraxofusp is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacodynamic data showed tagraxofusp affinity for IL3-R and antitumor activity *in vitro* and *in vivo* on BPDCN cells. The PK profile is well documented and supports its pharmacological and toxicological evaluations in the selected preclinical species. The toxicological program designed in accordance with ICH S9 guideline and ICH S6 guideline, allowed to identify main target organs toxicities in monkey. Most of the adverse effects showed in animals can be monitored in human.

Overall, it is considered that the toxicological package available with tagraxofusp is adequate for the proposed indication and is in line with ICH S9 and ICH S6 guidelines.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 18. Overview of clinical studies of tagraxofusp in patients with BPDCN

Study Title	Patient Population Studied	Comparator Control	Treatment Phase	Treatment Arms, Dosage Regimen, Route of Administration	Primary Objective(s)	Number of Patients	Study Status/ Data Cutoff Date
Study 50047							
Therapy targeting the IL-3R for patients with relapsed or refractory and elderly or poor-risk AML or high-risk MDS with DTIL3 (IND# 11314): a Phase I/II clinical trial	Patients with BPDCN, AML, MDS, or CML	NA	Phase 1/2	A 15-minute IV infusion of 4 to 22 µg/kg of tagraxofusp under 2 different dose/scheduling regimens: Regimen A: every other day dosing for up to 6 doses Regimen B: daily dosing for up to 5 doses	1. Determine the MTD 2. Identify a dose for subsequent disease-directed studies 3. Document DLTs of escalating doses of a single cycle of tagraxofusp	70 AML, 12 BPDCN, 7 MDS, and 3 CML patients	Complete

Study Title	Patient Population Studied	Comparator Control	Treatment Phase	Treatment Arms, Dosage Regimen, Route of Administration	Primary Objective(s)	Number of Patients	Study Status/ Data Cutoff Date
Study STML-401-0114							
SL-401[1] in patients with AML or BPDCN	Patients with BPDCN or AML	NA	Phase 1/2	A 15-minute IV infusion of escalating doses of at 7, 9, 12, and 16 µg/kg/day of tagraxofusp (the latter dose in in AML patients only) for 5 consecutive days	Stage 1: Determine the MTD or the MTeD where multiple DLTs were not observed Stage 2: Determine the efficacy of tagraxofusp in BPDCN patients, as assessed by ORR; characterize the safety profile of tagraxofusp at the MTD or MTeD in patients with AML and patients with BPDCN Stage 3: Determine the CR rate (CR+CRc) in patients with first-line BPDCN; characterize the safety profile of tagraxofusp in patients with first-line BPDCN	47 BPDCN patients, 49 AML patients	Ongoing/ 25 Sep 2017

Abbreviations: AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CML = chronic myeloid leukemia; CR = complete response; CRc = complete response with minimal residual skin abnormality; DLT = dose-limiting toxicity; DTIL3 = diphtheria toxin fused to interleukin-3; IL3R = interleukin-3 receptor; IND = investigational new drug; IV = intravenous; MDS = myelodysplastic syndrome; MTD = maximum-tolerated dose; MTeD = maximum-tested dose; NA = not applicable; ORR = objective response rate.

[1] SL-401 is the nonproprietary name for tagraxofusp.

Source: www.clinicaltrials.gov, (Frankel, 2014), Study 0114 CSR.

2.4.2. Pharmacokinetics

The clinical pharmacology investigations have been performed in 4 clinical studies of patients with haematological malignancies (AML, BPDCN, MM, HRMPN), BPDCN, where study STML-401-0114 is the pivotal study performed in both AML and BPDCN patients (Table 19).

Table 19. Clinical Pharmacology Studies

Study Identifier	Study Phase	Type of Study	Diagnosis of Patients	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients
STML-401-0114	1/2	Non-randomized, open-label, multi-stage, dose-escalation and expansion study	Patients with BPDCN or AML	Tagraxofusp Stage 1: 23 patients (9 BPDCN and 14 AML) were treated with Tagraxofusp Injection at doses of 7 (N=6), 9 (N=3), 12 (N=8), or 16 µg/kg/day (N=6; the 16 µg/kg/day dose was evaluated only in patients with AML). Stage 2-4: 73 (35 AML patients and 38 BPDCN) patients were treated at 12 µg/kg/day. For all stages, a cycle of therapy is 21 days. Tagraxofusp is administered as a 15-minute IV infusion for the first 5 consecutive days of a 21-day cycle. Tagraxofusp is supplied as Tagraxofusp Injection frozen solution (1 mg/mL) for Stages 1, 2, and 3. A lyophilized formulation (Tagraxofusp for Injection, lyophilized powder, for solution; 1 mg/mL) was supplied for dosing in selected patients with AML in Stage 2.	Stage 1: 23 patients Stage 2: 58 patients Stage 3: 13 patients Stage 4 (ongoing): 2 patients Data from 96 patients through 31 January 2018 are included in Study 0114 CSR. Updated efficacy data for 47 patients with BPDCN through 03 October 2018 are included Module 2.5.
STML-401-0214	1/2	Non-randomized, open-label, 2 stage dose-escalation study	Patients with adverse risk AML in first or second CR, with or without Evidence of Minimal Residual Disease (MRD) in First CR	Tagraxofusp Stage 1: 9 patients were treated with tagraxofusp at doses of 7 (N=3), 9 (N=3) or 12 (N=3) µg/kg/day for 5 consecutive days every 28 days Stage 2: 7 patients were treated at 12 µg/kg/day. Up to 20 patients with evidence of MRD as determined locally will be treated at the in Stage 2. Tagraxofusp is supplied as Tagraxofusp Injection frozen solution (1 mg/mL) and administered as a 15-minute IV infusion.	Stage 1: 9 patients Stage 2 (ongoing): 7 patients Data from 16 patients through 31 January 2018 are included in the application

Study Identifier	Study Phase	Type of Study	Diagnosis of Patients	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients
STML-401-0314	1/2	Non-randomized, open-label, 2 stage dose-escalation study	Patients with Advanced, High Risk Myeloproliferative Neoplasms	Tagraxofusp Stage 1: 9 patients were treated with tagraxofusp at doses of 7 (N=3), 9 (N=3)or 12 (N=3) µg/kg/day for 3 consecutive days every 21 days in Cycles 1-4, every 28 days in Cycles 5-7 and every 42 days in Cycle 8 and beyond Stage 2: 20 patients were treated at 12 µg/kg/day Approximately 60 additional patients with myelofibrosis or chronic myelomonocytic leukemia (18 each) will be treated in Stage 2. Tagraxofusp is supplied as Tagraxofusp Injection frozen solution (1 mg/mL) and administered as a 15-minute IV infusion.	Stage 1: 9 patients; Stage 2 (ongoing):20 patients Data from 29 patients through 31 January 2018 are included in the application
STML-401-0414	1/2	Non-randomized, open-label, 2-stage dose-escalation study	Relapsed or Relapsed and Refractory MM	Tagraxofusp, Dexamethasone, Pomalidomide Stage 1: 7 patients were treated with tagraxofusp at 7 µg/kg/day for 5 consecutive days every 28 days Stage 2: Approximately14 additional patients in Stage 2. Tagraxofusp is supplied as Tagraxofusp Injection frozen solution (1 mg/mL) and administered as a 15-minute IV infusion.	Stage 1 (ongoing): 7 patients Stage 2: up to 14 additional patients Data from 7 patients through 31 January 2018 are included in the application

Abbreviations: AML = acute myeloid leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm, CR = complete response, DLT = dose-limiting toxicity, IV = intravenous, MM = multiple myeloma, MRD = minimal residual disease, MTD = maximum tolerated dose.

Full PK sampling has been performed at several occasions. PK data from the four studies were pooled using a population PK analysis (independent of the indication). Exposure-response (ER) analysis was restricted to PK/PD data from BPDCN patients and all patients respectively for ER-efficacy and ER-safety.

Methods

- Bioanalysis

The applied analytical method to quantify free tagraxofusp in human plasma samples with K_2EDTA as anticoagulant, has been developed in two US sites and validated according to the FDA Guideline ("Bioanalytical method validation Guidance for Industry"). Pooled plasma for use as blank or control in assay methodology typically has anti-DT due to the near ubiquitous use of diphtheria immunization. Therefore, beagle plasma was employed as a surrogate matrix for preparation of standard curves. A cross-validation study has been performed between the two methods. Results of this analysis showed that between Eurofins and the two BDS sites more than 85% of the samples met the acceptance criteria whereas 100% of the samples show good agreement within BDS sites.

No study was performed to assess the extent of interferences coming from binding to target present in patients' plasma or parallelism of the analytical method.

- Anti-drug antibody analysis

Four distinct assays were developed and validated to support investigation of the immunogenicity of tagraxofusp in patients during clinical trials. These methods are summarised as follows:

1 Anti-tagraxofusp antibodies (**ADA**) were assessed and titre evaluated in an electrochemiluminescent (ECL) bridging immunoassay using the mesoscale discovery (MSD) system. This method captures antibodies formed towards both functional domains (DT and hIL3) of tagraxofusp and the method testing strategy included domain specificity binding characterisation involving competitive inhibition with hIL3 and DT separately.

2 Tagraxofusp neutralising antibodies (**NAb**) were assessed in a cell-based assay using IL-3 receptor expressing erythroleukemic cells (FT-1-Hras) that detect the presence of NAb in ADA positive samples by their ability to attenuate cytotoxicity induced by exogenous tagraxofusp. The resulting effect is assessed by measuring viability using a detection substrate. The assay design was based upon a cytotoxicity assay used to assess potency.

3 A direct-binding ELISA was used for specific detection and titre evaluation of antibodies to the hIL-3 domain (**AIA**) of tagraxofusp in patient sera as a robust antibody response to the DT domain of tagraxofusp had the potential to complicate detection of low levels of treatment-induced or treatment-boosted antibodies to human IL-3 (hIL) in the ADA assay.

4 The neutralising ability of the anti-hIL-3 antibody positive samples (**hIL-3 NAb**) were assessed in a cell-based assay in which growth factor dependent TF-1 cells are stimulated to proliferate by addition of hIL-3. If serum anti-hIL-3 antibodies are neutralising, the cells will exhibit decreased viability signal using a detection substrate.

The methods have been validated following recommendations in current guidelines and white papers and included cross testing to assess assay performance after assay transfer. All requirements and criteria stated in the protocol were met. The methods were found suitable for assessment of tagraxofusp immunogenicity. The drug tolerance established for all four methods were well above estimated serum levels of circulating tagraxofusp at the time of immunogenicity sampling.

Absorption

Bioavailability

Tagraxofusp is administered as an intravenous infusion.

Bioequivalence

The intended commercial formulation (frozen solution) has been used for the clinical studies included in this MAA. In study 0114, doses of 7, 9, 12, or 16 µg/kg tagraxofusp were administered via 15-minute intravenous infusion, using a frozen solution formulation. A small number of subjects received 15-minute infusions using a lyophilised powder formulation. Because of the small number of subjects who received the lyophilized powder formulation (N=7) and because of the large measurement variability in the data, no conclusions are made concerning the comparative PK of the lyophilized powder formulation and the frozen liquid formulation.

Distribution

The mean tagraxofusp volume of distribution is 5.1 L (SD of 1.9) in patients with BPDCN and have been estimated from 4 patients which were ADA negative at C1D1 as shown in Table 20 (PK values estimated in 4 patients : AUCinf, CL, Vz and T1/2; PK values estimated in 5 patients: Cmax Tmax, AUClast).

Table 20. Summary of PK parameters by Presence/absence of Pre-existing SL-401 ADA in subjects with BPDCN on C1D1

Anti-SL-401 ADA Status	Statistic	C_{max} (µg/L)	T_{max} (h)	AUC_{last} (h*µg/L)	AUC_{inf} (h*µg/L)	CL (L/h)	V_z (L)	$t_{1/2}$ (h)
Detected	Mean	80.3	0.317	96.1	150	13.9	21.2	1.18
	StD	81.1	0.0807	90.9	89.1	19.4	25.4	0.593
Not Detected	Mean	162	0.296	183	230	7.16	5.11	0.714
	StD	58.1	0.0270	130	123	7.19	1.86	0.337

Abbreviations: ADA = anti-drug antibodies; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last quantifiable observation; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CL = clearance; C_{max} = maximum concentration; StD = standard deviation; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum concentration; V_z = volume of distribution.
Source: STM0109 SL-401 NCA PK Report.pdf; Table 48

Immunogenicity

Of the 95 PK evaluable subjects only 5 had no detectable ADA at baseline.

Free SL-401 exposure showed a titer-dependant reduction with increasing ADA measured at baseline as shown in Table 21 below. A significant effect of ADA titer on C1D1 AUClast was observed ($p < 0.01$). Distribution of the titers was considerably shifted from C1D1 to C3D1.

Table 21. Free SL-401 Exposure by ADA Titer on C1D1 and C3D1 for 12 µg/kg/day

	AUC_{last} (h•µg/L)					
	Cycle 1 Day 1 (N = 77)			Cycle 3 Day 1(N = 31)		
ADA Titer	N	Mean	StD	N	Mean	StD
Not Detected	5	183	130	1	0.246	--
8	3	208	109	--	--	--
80	14	143	72.0	--	--	--
800	37	66.6	69.7	1	6.14	--
8000	17	31.0	56.1	2	0	--
80000	3	3.96	2.84	11	1.86	2.56
800000	--	--	--	18	0.989	2.20
8000000	--	--	--	2	0	--

Abbreviations: ADA = anti-drug antibodies; AUC_{last} = AUC from time 0 to last quantifiable observation; StD = standard deviation
Note: (Study 0114; September 25, 2017 Data Cutoff)
Source: STM0109 SL-401 NCA PK Report.pdf; Tables 59 and 61

Consequence of ADA titer on PK parameters is highlighted in Table 22 where, as ADA titer increases from ADA negative status to ADA positive (titer 800), Vz increased from 5.11 to 21.9 L.

Table 22. Free SL-401 Pharmacokinetic Parameters by ADA titer on C1D1 12µg/kg/day

	$t_{1/2}$ (h)		CL (L/h)		V_z (L)	
ADA Titer	Mean	StD	Mean	StD	Mean	StD
Not Detected	0.714	0.337	7.16	7.19	5.11	1.86
8	0.728	0.369	6.39	4.42	5.26	0.749
80	1.23	0.597	8.67	9.57	13.1	11.2
800	1.42	0.617	23.9	26.3	37.9	31.6
8000	1.32	0.412	12.2	6.83	21.9	10.4

Abbreviations: ADA = anti-drug antibodies; CL = clearance; StD = standard deviation; $t_{1/2}$ = terminal half-life; V_z = volume of distribution

Note: Total N = 50. No subject with titer of 80000 had an estimable terminal phase slope, precluding calculation of $t_{1/2}$, CL, and Vz.

Source: STM0109 SL-401 NCA PK Report.pdf; Table 63

Elimination

ADA negative

After end of infusion, SL-401 decreased rapidly following a monoexponential decline with a mean terminal half-life of 0.7 (SD 0.3) hours. Mean Clearance was estimated at 7.16 L/h (Table 12).

ADA positive

After accounting for ADA status, as ADA titer increase from ADA negative status to ADA positive (titre 800), terminal half-life, CL increased from 0.714 h to 1.32h and 7.16 to 12.2 L/h respectively.

Excretion

SL-401 is a recombinant fusion protein with a molecular weight of 58 kDa, which is considered to be degraded into amino acids.

Metabolism

No metabolite studies have been performed.

Dose proportionality and time dependencies

Dose proportionality

Formal dose proportionality could not be assessed due to significant titre-dependent influence of ADA and the variable distribution of ADA titre at baseline across the dose groups. Table 23 presents key exposure metrics for patients with BPDCN and AML (Study 0114).

Table 23. Free Tagraxofusp exposure following IV dose of 7,9,12 and 16 µg/kg on Day 1 and 5 of Cycles 1 and 3

		Tagraxofusp Daily Dose							
		7 µg /kg		9 µg /kg		12 µg /kg		16 µg /kg	
Exposure	Period	N	Mean (StD)	N	Mean (StD)	N	Mean (StD)	N	Mean (StD)
C_{max}	C1D1	6	29.1 (25.1)	3	12.2 (10.8)	79	66.4 (70.8)	7	78.5 (66.2)
µg/L	C1D5	6	94.7 (39.5)	3	64.3 (29.3)	39	77.1 (72.9)	1	93.8 (--)
	C3D1	4	22.4 (35.5)	2	20.8 (29.5)	36	2.42 (3.56)	1	37.3 (--)
	C3D5	3	33.1 (50.4)	1	0 (--)	39	1.52 (2.37)	0	-- (--)
AUC_{last}	C1D1	6	44.8 (36.9)	3	13.2 (15.4)	79	82.8 (88.1)	7	118 (103)
h•µg/L	C1D5	6	164 (90.3)	3	89.5 (3.94)	39	115 (111)	1	162 (--)
	C3D1	4	29.0 (54.2)	2	14.3 (20.2)	36	1.42 (2.46)	1	38.9 (--)
	C3D5	3	46.5 (79.7)	1	0 (--)	39	0.649 (1.24)	0	-- (--)

Abbreviations: AUC = area under the plasma concentration-time curve; C = Cycle, C_{max} = maximum concentration; D = Day; StD = standard deviation
Note: -- indicates not calculable

From 7 to 16 µg/kg at C1D1, Cmax increased with dose from 29.1 to 78.5 µg/L except for the dosing group (9 µg/kg) which is highlight on Figure 1, AUClast increased too with dose from 44.8 to 118 µg.h/L.

Time dependency

According to Table 23, for all dosing groups (7/9/12/16 µg/kg) both exposure parameters AUClast and Cmax increased between C1D1 to C1D5. For the 12 µg/kg dosing groups Cmax increased from 66.4 to 77.1 µg/L and AUClast from 82.8 to 115 µg.h/L.

However, between C1D1 and C3D1, both exposure parameters AUClast and Cmax were decreased from 66.4 to 2.42 µg/L and 82.8 to 1.42 µg.h/L, likely due treatment boosted or treatment emergent ADA.

For patients with BPDCN, Table 24 summarises key exposure metrics for free SL-401 concentration following IV dose of 12 µg/kg/day, whereas Table 25 lists a summary of key disposition parameters.

Table 24. Free SL-401 exposure following IV dose of 12 µg/kg/day in Patients with BPDCN

Exposure	Period	N	Mean	StD
C_{max}	C1D1	43	89.7	82.5
µg/L	C1D5	18	60.4	60.7
	C3D1	32	2.33	3.59
	C3D5	35	1.29	2.16
AUC*	C1D1	43	106	98.4
h•µg/L	C1D5	18	93.3	102
	C3D1	32	1.42	2.52
	C3D5	35	0.581	1.15

Abbreviations: AUC = area under the plasma concentration-time curve; BPDCN = blastic plasmacytoid dendritic cell neoplasm; C = Cycle, C_{max} = maximum concentration; D = Day; StD = standard deviation
*AUC is AUC_{last}. -- indicates not calculable
Sources: STM0109 SL-401 NCA PK Report.pdf; Tables 44-47

Table 25. Free SL-401 Pharmacokinetics parameters following IV dose of 12 µg/kg/day in Patients with BPDCN

		$t_{1/2}$ (h)		CL (L/h)		Vz (L)	
Period	N*	Mean	StD	Mean	StD	Mean	StD
C1D1	29	1.12	0.583	13	18.3	19.0	24.2
C1D5	14	0.988	0.326	38	39.9	39.7	32.8

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; C = Cycle, CL = clearance; D = Day; StD = standard deviation; $t_{1/2}$ = terminal half-life; V_z = volume of distribution
*Number of patients for whom a terminal phase slope could be estimated
Sources: STM0109 SL-401 NCA PK Report.pdf, Tables 44 and 45

The data showed a large variability between the first and following doses, which is a result of measuring the free tagraxofusp and the presence of pre-existing and treatment emerging or boosted ADAs.

Intra- and Inter-individual variability

For patients with BPDCN, irrespective of the ADA status, at C1D1 the %CV was 92% for Cmax and 92.7% for AUClast. The %CV was 141 % for CL and 127% for Vz. For patients with BPDCN, ADA negative, at C1D1 the %CV was 35.8% for Cmax and 71% for AUClast. The %CV was 100% for CL and 36.4% for Vz.

No stratification by target level was performed due to the unavailability of a suitable analytical method.

Pharmacokinetics in target population

Study STML 401 0114

Study STML 401 0114 was a Phase I/II non-randomized, open-label, multistage, dose-escalation and expansion study in patients with BPDCN or AML. At enrolment cut-off (17 Mar 2017), 96 patients had been recruited.

Tagraxofusp was administered as a 15-minute IV infusion for the first 5 consecutive days of a 21-day cycle. Tagraxofusp was supplied as frozen solution (1 mg/mL) for Stages 1, 2, and 3. A lyophilised formulation (lyophilised powder, for solution; 1 mg/mL) was supplied for dosing in selected patients with AML in Stage 2 and is planned for treatment of BPDCN patients enrolled in Stage 4.

The stages were carried out as follows:

- Stage 1: 23 patients (9 BPDCN and 14 AML) were treated with Tagraxofusp Injection at doses of 7, 9, 12, or 16 µg/kg/day for 5 consecutive days every 21 days. The 16 µg/kg/day dose was evaluated only in patients with AML.
- Stage 2: 58 (35 AML patients and 23 BPDCN) patients were treated at 12 µg/kg/day, the MTD, at which multiple DLTs were not observed during Stage 1.
- Stage 3: 13 first-line BPDCN patients were treated at 12 µg/kg/day and contribute as the pivotal cohort.
- Stage 4: 2 BPDCN patients were enrolled as of 17 Mar 2017.

The results referred to here are for the BPDCN population only, unless noted otherwise.

Plasma concentrations generally showed rapid monoexponential decline post end of infusion. Individual profiles showed considerable heterogeneity in Cmax and the slope of the terminal phase of the concentration-time profile. Across all dose levels, many patients had free tagraxofusp concentrations

below the limit of quantitation by 4 hours post dose on C1D1. NCA analysis at C1D1 and C1D5 showed increased and highly variable CL and Vz after 5 days.

Population PK analysis

An integrated PPK analysis was performed using concentration-time data from all 4 clinical studies of tagraxofusp. The objectives of the PPK analysis were to: 1) characterise the PPK of free tagraxofusp in patients with AML, BPDCN, relapsed/refractory (R/R) multiple myeloma (MM), or advanced, high-risk myeloproliferative neoplasms (MPN); 2) estimate the between subject and residual variability in free tagraxofusp PK; 3) quantify the magnitude of influence of pre-specified covariates on the disposition of free tagraxofusp; and 4) to assess the association of ADA (per ECL-IA methodology) and the PK of free tagraxofusp. For the purposes of the population PK analysis, the term ADA refers to total ADA (DT-related immune responses (pre-existing, anamnestic, and treatment-induced) and induced IL-3-related immune response).

The total dataset was divided into three windows: C1D1 data; C1D3-5 data, with day 3 data coming solely from study 0314; cycle 3 or 4 (C3-4) data (days 1, 3, or 5). C1D3-5 data was used as the reference dataset, given the assumption that ADA was less impactful during this treatment period.

The SL-401 PK data set was comprised of 127 patients (study 0114 n = 96; study 0214 n = 11; study 0314 n= 15, study 0414 n = 5), contributing a total of 2920 SL-401 observations. There was a large number of below limit of quantitation (BLQ) observations across the four studies (1360 records total, 1049 records in study 0114, 144 records in study 0214, 149 records in study 0314, and 18 records in study 0414), which is almost half of the total number of PK observations. The majority of BLQs occurred in treatment cycles 3 or 4 (for study 0314).

The final and most parsimonious model for describing the PK of free SL-401 was a one-compartment model with linear clearance. Table 26 shows the PK parameters resulting from this analysis for the different studies. Free SL-401 pharmacokinetics appeared to be dose-linear across the range of doses and regimens studied. V/F and CL/F increased with baseline weight.

Table 26. Summary of Population Pharmacokinetic Parameters by Study

	Clearance (L/h)		Volume (L)		Half-Life (h)	
Study	Median	StD	Median	StD	Median	StD
0114	42	140	46	180	0.98	0.53
0214	32	120	39	130	1.0	0.63
0314	18	51	25	67	0.99	0.75
0414	5.5	64	11	35	0.95	0.82

Source: Metrum Research Group Report STM0106F, Table 22

The PK model also included estimation of the fraction of dose escaping immediate ADA binding in plasma (F1). In this context, immediate binding refers to any binding occurring prior to the first PK sample, leaving less free drug available for venous sampling. The analysis was done in step-wise fashion, separately analyzing the three data windows mentioned above (C1D1, C1D3-5, C3-4), with the same one-compartment model. Model diagnostic plots indicated general GOF across the data windows.

According to the C1D3/5 model, the fraction of dose escaping immediate binding in plasma, F1, was 0.50, 0.14, and 0.13 for ADA baseline titres of 800, 8000, and 80000, respectively. Based on model

implementation, these values are estimated relative to a titre of 80 (which was fixed at a value of F1 = 1). Table 27 shows the estimates of F1 for C1D3/5 as well as for C1D1 and Cycle 34. Regardless, the estimates reinforce the marked impact of pre-existing, treatment-boosted, and/or treatment-emergent ADA on exposure.

F1 decreased with increasing titer within a given time period, since greater presence of ADA increased the immediate ADA binding of SL-401. For a given titer level, F1 also decreased for individuals at C1D1 or C3-4, relative to C1D35, since there was greater impact of ADA on free SL-401 exposure during these time periods.

Table 27. Population Pharmacokinetic Model Estimates of the Relative Fraction of Dose Escaping Immediate ADA Binding: Cycle 1 Days 3 and 5, Titer 80 Reference Condition

	C1D1[a]		C1D3/5b		C3-4[c]	
ADA Titer	N	F1	N	F1	N	F1
1‡	4	1.037	--	--	2	0.064
8	3	1.159	--	--	--	--
80	22	0.610	12	1*	--	--
800	64	0.192	39	0.500	5	0.196
8000	20	0.094	16	0.140	4	0.012
80000	3	0.103	3	0.130	17	0.007
800000	--	--	--	--	30	0.009

Abbreviations: ADA = anti-drug antibody; C = Cycle, D = Day; F1 = fraction of dose a For C1D1, F1 is calculated relative to F1 for ADA Titer =80 at C1D3/5 (Model 2300) and the model estimated F1 offset parameters for C1D1 (Model 2294). b For C1D3/5, F1 is calculated relative to F1 reference at ADA Titer = 80, which is fixed to a value of 1 (Model 2300). c For C34, F1 is calculated relative to F1 for ADA Titer =80 at C1D3/5 (Model 300) and the model estimated F1 offset parameters for C34 (Model 308). ‡Titer = 1 is defined as subjects with undetectable anti-tagraxofusp ADA. *Titer = 80 on C1D3/5 represents the reference condition all other F1 values are estimated relative to. Sources: Table derived from Metrum Report STM0106F, Tables 20, 22, 23 [Models 308 (C34), 300 (C1D3/5), 2003 (C1D3/5), and 2294 (C1D1)]

Special populations

Impaired renal function

No formal study were submitted to evaluate the impact of renal impairment on SL-401 PK. Based on the results of the PopPK analysis (Reference Model C1D3-5), the population clearance CL/F at the chosen reference ADA titre of 80 was 3.7 L/h (RSE of 80%). CL/F decreased with eGFR (normalised to 83 mL/min) according to a power model with exponent estimate of 0.25 (140% RSE). For patients with mild (eGFR = 60-89 mL/min) or moderate (eGFR = 30-59 mL/min), no clinically meaning full changes in free tagraxofusp AUC were expected. Estimated eGFR ranged from 42 to 158 mL/min/1.73 m^2 in the dataset, representing a relatively broad range of renal function.

No data are available for patients with severe renal impairment or end-stage renal disease.

Impaired hepatic function

No formal study were submitted to evaluate the impact of hepatic impairment on SL-401 PK.

The influence of mild hepatic impairment based on the National Cancer Institute-Organ Dysfunction Working Group [NCI-ODWG] criteria was evaluated in a post-hoc analysis. The mild impairment group

included 2 subjects with moderate impairment on C1D1. For C1D1, the estimate of the hepatic impairment effect was 60% increase in clearance with a 95% CI (0-140%).

For C1D3-5, the estimated hepatic impairment effect in tagraxofusp clearance was 98% with a 95%CI of 83-120% which include the 100% value. No effect of hepatic impairment on SL-401 clearance is expected.

Gender

A post-hoc exploratory analyses of the EBE of patient specific clearance random effects from the reference PK model (C1D3-5) was performed. In this exploratory assessment, there was no appreciable difference between males and females.

Race

Results from the PopPK analysis indicated that race seems to have no impact on the available PK parameters.

Weight

In the primary reference model describing C1D3/5 PK (Metrum Report STM0106F, Table 18, Model 334), the population CL at the chosen reference ADA titre of 80 was 3.7 (80% relative standard error [RSE]) L/h. Clearance increased with body weight (normalised to 70 kg) according to an allometric relationship with exponent estimate of 0.99 (78% RSE).

Based on a population pharmacokinetic analysis of free tagraxofusp plasma concentrations following the first dose of Elzonris, no clinically meaningful changes in free tagraxofusp exposure are expected with respect to bodyweight.

Elderly

Results from the PopPK analysis indicated that age was not a significant covariate of any of the available PK parameters

Pharmacokinetic interaction studies

No interaction studies have been performed (see discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

No studies have been performed (see discussion on clinical pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

Tagraxofusp (SL-401, DT388IL3) is intended for treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) and other haematological malignancies where CD123 is expressed. It is a 524-amino acid recombinant fusion protein expressed in Escherichia coli, composed of interleukin-3 (IL-3) and truncated diphtheria toxin (DT, the binding domain of DT is absent). DT inhibits protein

synthesis and induces apoptosis in cells expressing the interleukin 3 receptor (IL-3R) which is the molecular target for tagraxofusp. Binding of tagraxofusp to IL-3R leads to internalisation of the complex and localisation to endosomes where endosomal furin releases the catalytic domain of DT. The free catalytic domain of DT enters the cytosol via the translocation domain and inactivates cellular protein synthesis by ADP-ribosylating the diphthamide residue in domain IV of elongation factor 2 (a key protein involved in protein translation). This halts protein synthesis and triggers a series of cellular events that culminates in apoptosis of the intoxicated cell.

The protein is engineered such that the IL-3 domain replaces the native receptor binding domain of DT. The applicant claims that tagraxofusp are thereby able to target cells that express CD123 (the alpha subunit of IL-3R). CD123 is expressed on both the tumour bulk and cancer stem cells of multiple haematological malignancies, including BPDCN and AML, but has limited expression on normal tissue.

Primary pharmacology

Exploratory graphical analysis on the PD end-points neutrophils and bone marrow blasts, and efficacy end-point mSWAT, was conducted to assess relationships between tagraxofusp exposure and efficacy endpoints in subjects with BPDCN, and to also assess the impact of the presence of neutralising ADAs against tagraxofusp on the exposure-efficacy relationships.

The objective of the analyses was to develop an understanding of the underlying tagraxofusp E-R relationships for biomarker, efficacy, and safety endpoints in BPDCN and other hematologic malignancies. The following biomarker, efficacy and safety measures were analysed in this work:

- Biomarkers: peripheral blood neutrophil count, blast percentage in bone marrow.
- Clinical efficacy endpoints: best overall response (BOR) of complete response (CR) or CR clinical (CRc), defined as CR with minimal residual skin abnormality, duration of CR/CRc response (DOR), and modified severity weighted assessment tool (mSWAT: Extent of skin involvement as measured by mSWAT).
- Adverse events (AEs): hypoalbuminemia, transaminase elevations, and Capillary Leak Syndrome (CLS), as captured in adverse event reporting.
- Laboratory abnormalities: laboratory values for albumin and transaminase elevations based on samples collected in Cycle 1 and graded in a manner consistent with Common Terminology Criteria for Adverse Events (CTCAE) criteria.

The PK-efficacy and PK-safety analyses are described below in the section Relationship between plasma concentration and effect.

Methods

The following efficacy responses and best response values were determined for bone marrow blasts, mSWAT and peripheral blood neutrophils:

- Responses at reference time points are referred to as "landmark" response values. Landmark absolute change from baseline values were computed at reference time points corresponding to the end of Cycles 1, 2, and 4.
- For each subject and for each endpoint, the best response value (expressed as change from baseline) was computed based on data from all cycles. The PK/PD data set contained baseline values for each endpoint; these baseline values were obtained from the source data using records labelled as a baseline visit.
- Neutrophils were sampled more frequently within the treatment cycles compared to the other two endpoints. For analysis purposes, the end of cycle assessment for neutrophils was based on the last observation within the treatment cycle, with the condition that it must be at least 10 days

after the last dose in the cycle in order to minimize the impact of steroid-induced neutrophil increase following the protocol specified co-administration of steroids prior to infusion of tagraxofusp.

Neutralising antibody was evaluated using a covariate named PERNAB in the PK/PD data set. This variable represented observed/imputed percent neutralising antibody for tagraxofusp. Imputation was carried out using a last observation carried forward method. In some instances the observed percent neutralising antibody exceeded 100%, which can be explained by differences in the proliferation response of the cell populations used in the bioassay.

The following graphical displays were generated for each endpoint:

- Observed data (all cycles) vs. time
- Observed change from baseline (all cycles) vs. time
- Best response as change from baseline vs. AUC0-24hr and Cmax (Cycle 1, Days 1 and 5)
- End of Cycle 1 change from baseline vs. AUC0-24hr and Cmax (Cycle 1, Days 1 and 5)
- End of Cycle 1 change from baseline vs. percent neutralising antibody
- End of Cycle 2 change from baseline vs. AUC0-24hr and Cmax (Cycle 1, Days 1 and 5)
- End of Cycle 2 change from baseline vs. percent neutralising antibody
- End of Cycle 4 change from baseline vs. AUC0-24hr and Cmax (Cycle 1, Days 1 and 5)
- End of Cycle 4 change from baseline vs. presence or absence of detectable tagraxofusp levels in Cycle 3
- End of Cycle 4 change from baseline vs. percent neutralising antibody

Bone marrow blasts

Individual time-profiles of bone marrow blasts response are shown in Fig 3. The figure demonstrated large inter-individual variability in response over time, but three distinct profiles were extracted from the data. Blasts percentages typically decreased from baseline to end of Cycle 1 and then remained relatively constant in subsequent cycles. A subset of subjects showed an initial decrease in blasts during Cycle 1 followed by an increase and return towards baseline at later cycles. Another subset of subjects, generally those with low baseline blasts, exhibited a minimal change from baseline over time. Best response vs. Cycle 1, Day 1 $AUC_{0\text{-}24hr}$ were conditioned by observed quartiles of baseline blasts. No apparent E-R relationship was observed, even if subjects in the highest quartile showed the largest reduction in blasts percentage from baseline.

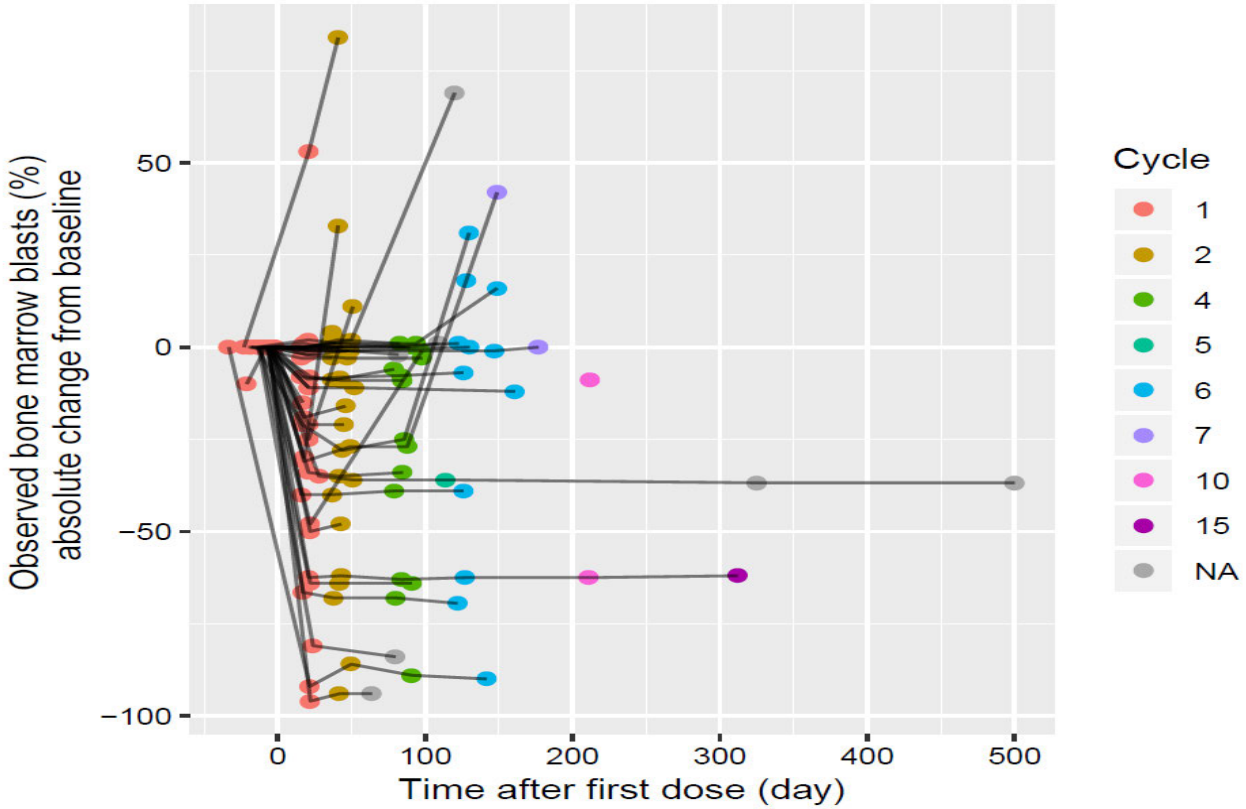


Figure 2. Bone marrow blasts: observed change from baseline vs. time

Observed change from baseline is plotted vs. time after first dose. Closed circles indicate observed values with individual data connected by black lines. Cycle NA = missing cycle number

Impact of neutralising antibodies

Plots of change from baseline in Cycle 2 versus percent neutralising antibody are shown in fig 5.

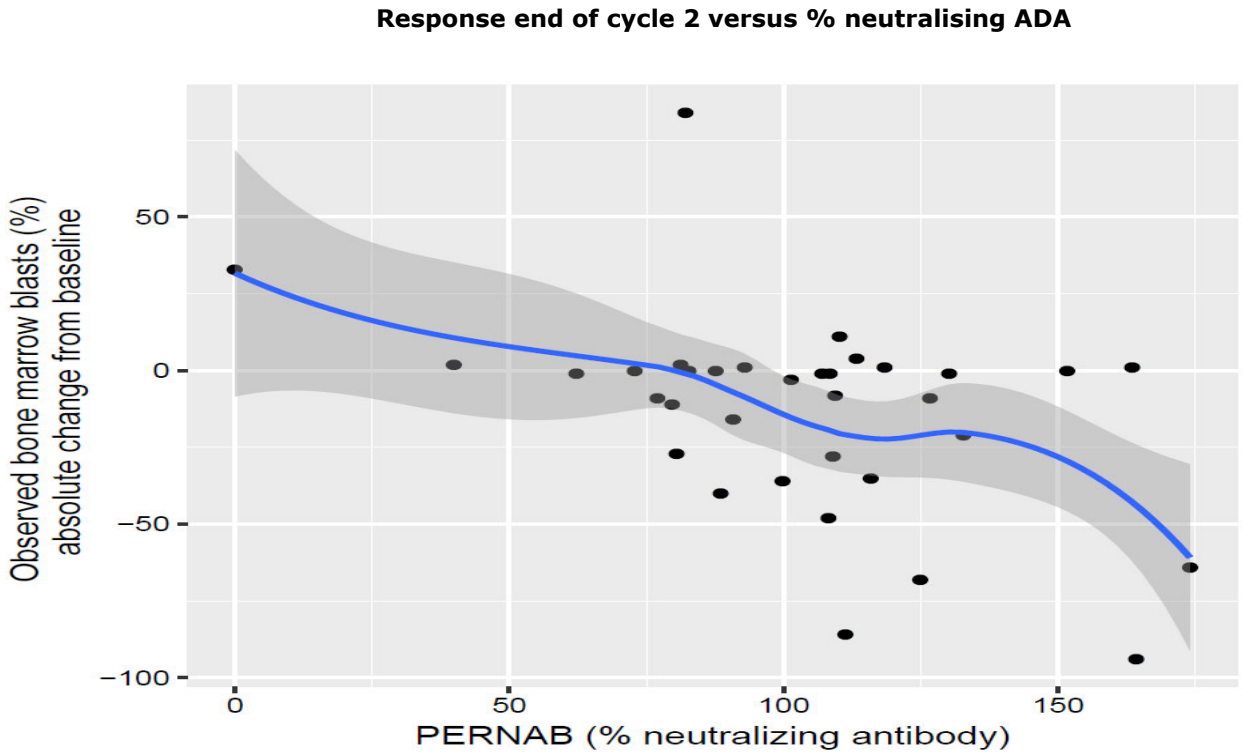


Figure 3. Bone marrow blasts: end of cycle 2 response vs. neutralising antibody

Observed change from baseline at end of cycle 2 is plotted vs. PERNAB. PERNAB is a covariate in the data set representing imputed/observed percent neutralising antibody for tagraxofusp. Imputations were performed using last observation carried forward. Closed black circles represent individual data and the blue line depicts an approximate value through the data with a 80% CI (shaded grey region).

No apparent relationships between response and neutralising antibody were observed. Regarding presence or absence of detectable tagraxofusp levels in Cycle 3; subjects with no detectable levels still showed a reduction in blasts of similar magnitude to subjects with quantifiable tagraxofusp concentrations.

Peripheral blood neutrophils

Individual time-profiles of peripheral blood neutrophil responses (change from baseline) are shown in fig. 5. The figures showed large inter-individual variability in response over time, but three distinct profiles were extracted from the data: 1) steady increase in neutrophils over the treatment cycles; 2) initial decrease in neutrophils followed by a return towards baseline at later cycles; and 3) minimal change from baseline over time.

Best response vs. Cycle 1, Day 1 $AUC_{0\text{-}24hr}$ were conditioned by observed quartiles of baseline neutrophils. The effect size, unlike that observed with bone marrow blasts and mSWAT, did not appear to be related to baseline values of the endpoint.

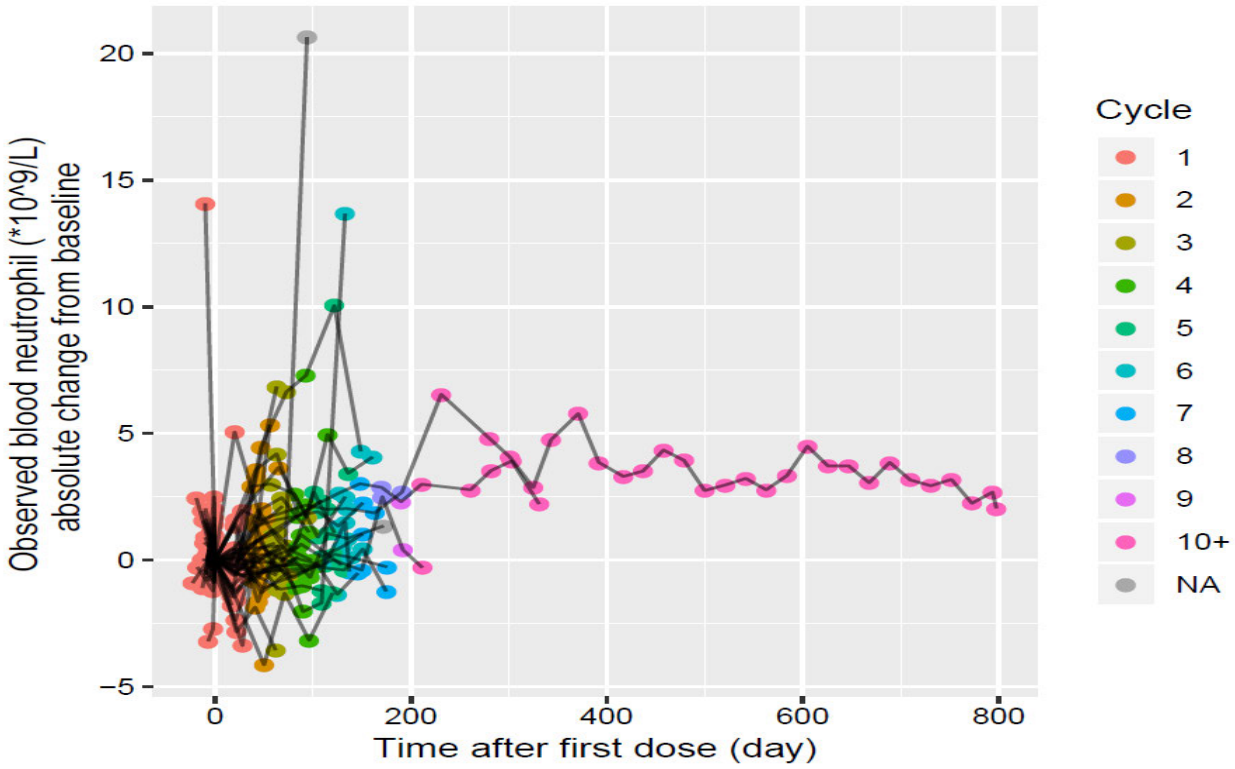


Figure 4. Peripheral blood neutrophils: observed change from baseline vs. time

Observed change from baseline is plotted vs. time after first dose. Closed circles indicate observed values with individual data connected by black lines. Cycle NA = missing cycle number.

Plots of change from baseline in cycle 2 vs. percent neutralising antibody are shown in fig 6.

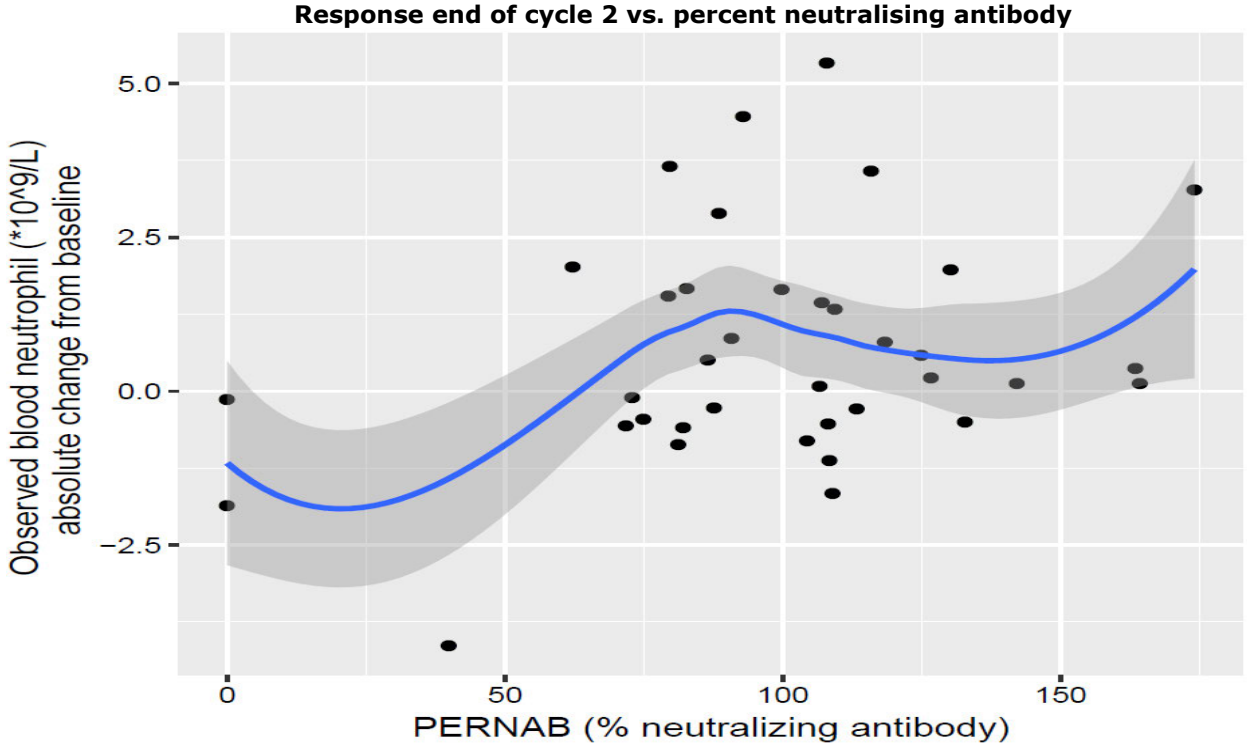


Figure 5. Peripheral blood neutrophils: end of cycle 2 response vs. neutralising antibody

Observed change from baseline at end of cycle 2 is plotted vs. PERNAB. PERNAB is a covariate in the data set representing imputed/observed percent neutralizing antibody for tagraxofusp. Imputations were performed using last observation carried forward. Closed black circles represent individual data. Blue line is a loess smooth through the data with a 80% CI (shaded grey region).

No apparent relationships between response and neutralising ADAs were observed in this or any of the cycles. Subjects with no detectable tagraxofusp showed an increase in neutrophils of similar magnitude to subjects with quantifiable tagraxofusp concentrations.

Modified severity weighted assessment tool (mSWAT)

The mSWAT score is a composite scoring system that characterises the skin involvement of three different lesion types. Patch, plaque and tumour body surface area are determined and multiplied by a factor of 1, 2 and 4, respectively, to establish the mSWAT subtotals (the mSWAT score equals the summation of these subtotals).

Individual time-profiles of mSWAT response (change from baseline) are shown in fig 7. There was large inter-individual variability in response over time, but three distinct profiles substantiated. mSWAT typically decreased from baseline to end of Cycle 1 and then remained relatively constant in subsequent cycles. A subset of subjects showed an initial decrease in mSWAT during Cycle 1 followed by an increase and return towards baseline at later cycles. Another subset of subjects, generally those with low baseline mSWAT (near 0%), exhibited a minimal change from baseline over time.

Best response vs. Cycle 1, Day 1 AUC0-24hr were conditioned by observed quartiles of baseline mSWAT. No apparent E-R relationship was observed. The effect size did appear to be related to baseline mSWAT, as subjects in the highest quartile showed the largest reduction in mSWAT from baseline.

The potential impact of the dominant lesion type on the ER relationship was investigated by conditioning the E-R plots for mSWAT by the dominant lesion type at baseline. No apparent E-R relationship was observed within each lesion type, but subjects with dominant lesions of the plaque or tumour type tended to have larger reductions in mSWAT score vs. subjects with a patch manifestation. Dominant lesion type was a variable obtained directly from the source data (i.e. it was not derived in any post-hoc fashion).

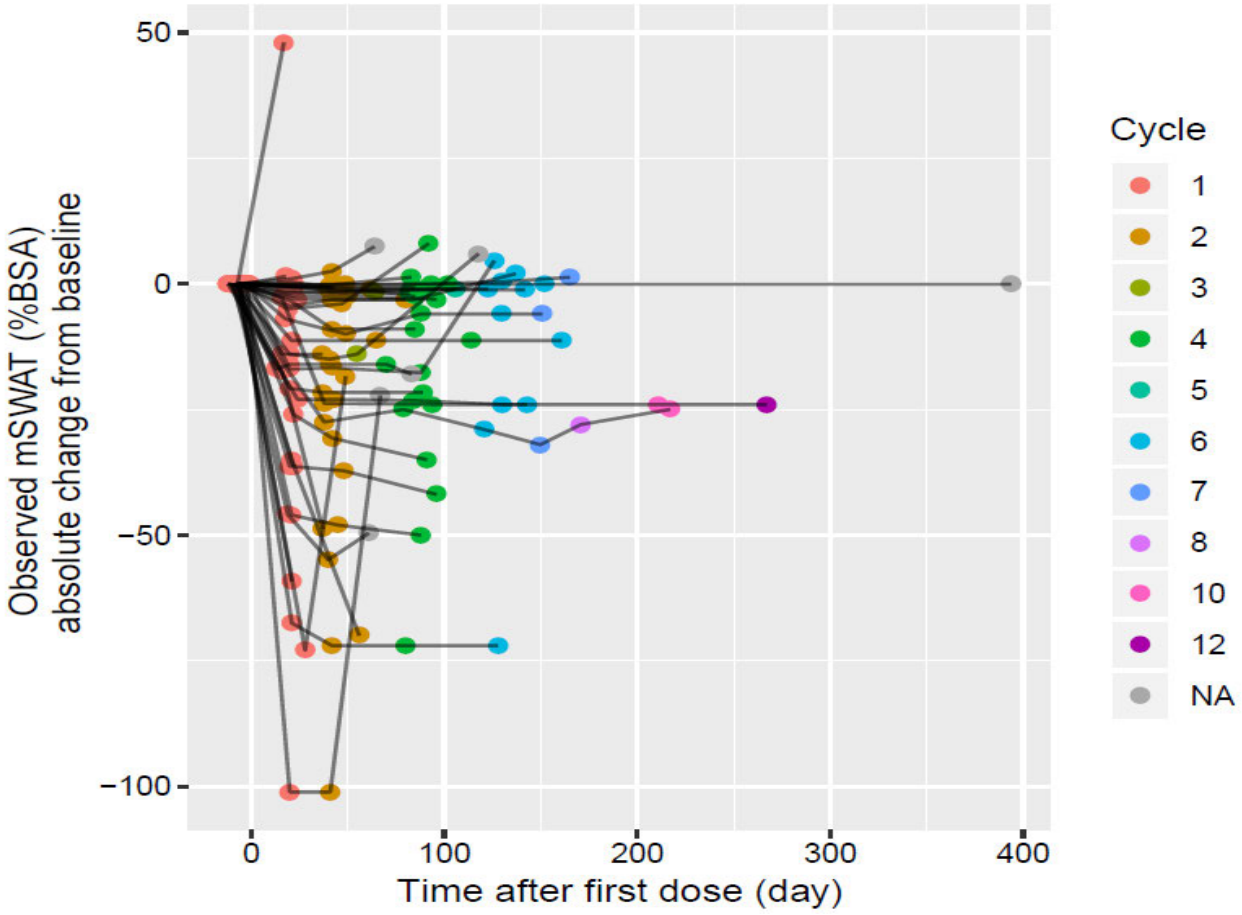


Figure 6. mSWAT: observed change from baseline vs. time

Observed change from baseline is plotted vs. time after first dose. Closed circles indicate observed values with individual data connected by black lines. Cycle NA = missing cycle number.

Plots of change from baseline in Cycle 2 versus percent neutralising antibody are shown in fig 8.

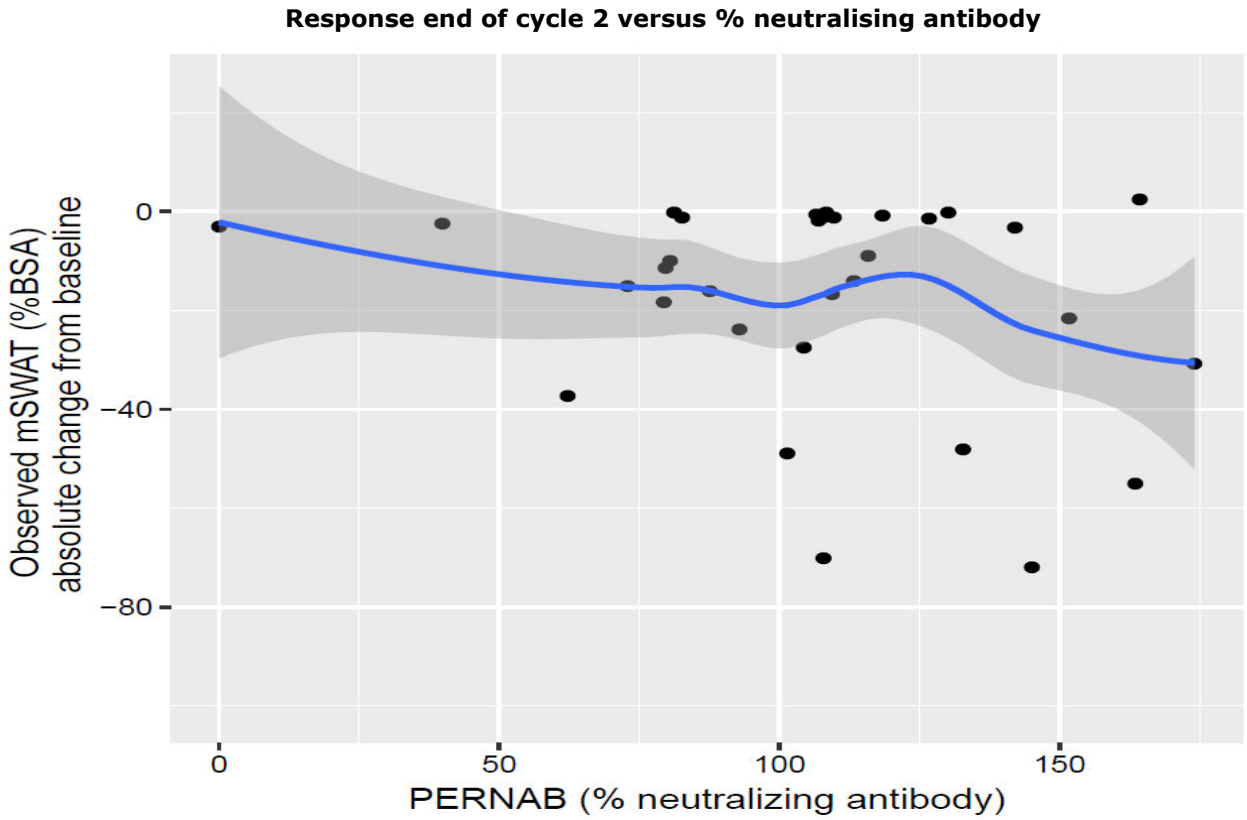


Figure 7. mSWAT: end of cycle 2 response versus neutralising antibody

Observed change from baseline at end of cycle 2 is plotted vs. PERNAB. PERNAB is a covariate in the data set representing imputed/observed percent neutralising antibody for tagraxofusp. Imputations were performed using last observation carried forward. Closed black circles represent individual data. Blue line is a loess smooth through the data with an 80% CI (shaded grey region).

No apparent relationships between response and neutralising antibody were observed. The change from baseline in Cycle 4 vs. the presence or absence of detectable tagraxofusp-levels in Cycle 3 were plotted. Subjects with no detectable tagraxofusp still showed a reduction in mSWAT and of similar magnitude to subjects with quantifiable tagraxofusp concentrations.

Secondary pharmacology

QTc/exposure analysis

A QTc/exposure analysis was performed using data from Study 0114 to evaluate the relationship between tagraxofusp concentrations and duration of the Fridericia corrected QT interval (QTcF), the duration of the RR interval, and whether ADAs alter the relationships between tagraxofusp concentration and ECG metrics.

The E-R analysis dataset comprised data from 96 patients. Patient ages ranged from 21 to 87 years and 29% of patients were female. Eight-three percent (83%) were administered doses of 12 µg/kg/day and 48% were BPDCN patients. Seventy-seven percent (77%) had a least one neutralising ADA positive measurement. Although 96 patients are included in the data set, only 95 had QT interval measurements reported.

Table 28 summarises key characteristics of the 95 analysed patients.

Table 28. Demographic summary: key characteristics of the 95 analysed patients

		$N = 95$
Age	y	21.0 65.0 87.0 (62.4 ±14.7)
Weight	kg	56.9 82.2 162.4 (83.6 ± 17.2)
Sex		
F		29% (28)
M		71% (67)
Race		
AMERICAN INDIAN OR ALASKA NATIVE		1% (1)
ASIAN		3% (3)
BLACK OR AFRICAN AMERICAN		3% (3)
OTHER		3% (3)
WHITE		89% (85)
Cancer Type		
BPDCN		48% (46)
PERSISTENT OR RECURRENT AML		52% (49)
Arm		
7 μg/kg/day		6% (6)
9 μg/kg/day		3% (3)
12 μg/kg/day		83% (79)
16 μg/kg/day		7% (7)

a b c represent the minimum a the median b and the maximum c for continuous variables.
x ±represents $\bar{X}$ ±1 SD. Numbers after proportions are frequencies.

The fixed effect estimates and bootstrapped 95% confidence interval (CI) indicate that tagraxofusp is not associated with a concentration-dependent prolongation of the QTcF interval (at the highest maximum tagraxofusp Study 0114, 353 µg/L, the expected ΔQTcF would be -16.6 ms (353 µg/L × -0.0469 ms/µg/L). The RR interval duration appears to shorten (heart rate increases) in a concentration-dependent manner (Table 29).

Table 29. Summary of concentration slope estimates for QTcF and RR Intervals, with Bootstrap Confidence Intervals

ECG Endpoint	Slope Estimate (ms/µg/L)	Bootstrap 95% CI
QTcF	-0.0481	(-0.102, 0.00858)
ΔQTcF	-0.0469	(-0.102, 0.0103)
ΔQTcFcyc	-0.0428	(-0.0928, 0.00911)
RR	-0.767	(-1.08, -0.448)
ΔRR	-0.840	(-1.18, -0.519)
ΔRRcyc	-0.877	(-1.16, -0.587)

Abbreviations: Δ = change; CI = confidence interval; ECG = electrocardiogram; QTcF = corrected QT interval using Fridericia's equation.

Impact of anti-drug antibodies

Evaluation of the influence of ADA neutralising antibodies on QTcF and RR intervals was performed via examination of graphical diagnostics, including weighted residuals and empirical Bayesian estimates of patient-specific slope estimates. No trend in either of these diagnostics with respect to either the dichotomous present/absent or the continuous percent neutralisation variable. Neutralising anti-tagraxofusp antibodies (NAbs against hIL3 was not modelled, due to limited number of samples) did not show any apparent impact on the relationship between tagraxofusp concentration and any of the ECG endpoints.

Relationship between plasma concentration and effect

The association of free tagraxofusp exposure and 1) efficacy in BPDCN, 2) safety in multiple haematologic malignancies, and 3) biomarkers in BPDCN was evaluated in a comprehensive model-based population analysis (see above). For the exposure-efficacy analyses, only responses from patients with BPDCN were used, as that is the subject indication of this application. Thus, the analyses only employ data collected in Study 0114. The safety analyses pool data across the three monotherapy studies of tagraxofusp (Studies 0114, 0214, and 0314). Summaries of the efficacy and safety analyses are described separately below. Exploratory efficacy and biomarker analyses were also conducted for blast percentage in BM, mSWAT, and peripheral blood neutrophil counts (see above).

Tagraxofusp ER for Efficacy endpoints

The objectives of these analyses were to characterize the E-R relationship for the probability that best overall response (BOR) was complete response (CR) and the duration of response (DOR) for CR. BOR was defined for each subject as the best response over the course of the study, with ordering as follows: CR+CRc > Cri > partial response > stable disease > progressive disease/relapse. The tagraxofusp exposure metrics to be evaluated in the analysis included the PopPK model predicted Cmax in the dosing interval on C1D1 and AUC0-24 following C1D1 dose. AUC0-24 was evaluated as a continuous measure, however for graphical and model diagnostic purposes only, AUC0-24 was divided in three bins (0-25 / 25-100 / > 100 µg.h/L).

Associations between clinical response and metrics of exposure (both C1D1 AUC0-24 and Cmax) were assessed graphically and summarised qualitatively. Associations between BOR of CR+CRc and AUC0-24 were quantified via a multiple-predictor logistic regression model. In addition to exposure, candidate covariates evaluated for inclusion in the model were the stage of therapy (first line vs. relapsing/recurring), the baseline extent of skin involvement, the dominant skin lesion type, the presence or absence of quantifiable tagraxofusp in Cycle 3, and the presence or absence of ADA neutralizing antibodies in Cycles 1 and 3. Least absolute shrinkage and selection operator (LASSO) methodology for selection of important covariates was employed. Based on exploratory analysis, increasing incidence of BOR of CR+CRc was associated with increasing both AUC0-24 and Cmax. Since Cmax and AUC0-24 is highly correlated, AUC0-24 was selected as the exposure metric for modelling.

On the basis of the multiple-predictor logistic regression model with LASSO covariate selection, C1D1 AUC0-24 was estimated to increase the odds of a BOR of CR+CRc by approximately 2.9x per 100 µg.h/L. However, this association was not significant at the level of 0.05 when applying asymptotic standard errors (95% CI include the value 1).

A Markov multistate (longitudinal) model for clinical response was developed and used as the basis for predictive inferences regarding DOR. 4 states were defined:

- State 1: All on study assessment that were not CR or CRc. All subjects were classified as belonging to State 1 at baseline
- State 2: All assessment of CR or CRc
- State 3: Assessment with transition to progressive disease
- State 4: All censoring events not associated with progressive disease

The exposure-response analysis for DOR, showed that higher C1D1 AUC0-24 was associated with a 0.549x reduction in the hazard of transitioning from State 2 to State 3, however this effect was estimated with a highly variable precision. The model-predicted mean DOR varied from 278 days to 590 days depending on C1D1 exposure category and whether there was quantifiable tagraxofusp in Cycle 3.

Tagraxofusp ER for Safety endpoints

The objectives of the analysis were to characterise the relationship between tagraxofusp exposure and treatment-emergent AEs of hypoalbuminemia, elevations of transaminases, and CLS in patients with hematologic malignancies. The analysis of AEs included 2 approaches with different definitions of AEs. One approach used AES captured and coded according to preferred terms. The other approach extracted laboratory abnormalities and applied CTCAE criteria for determination of AE and severity.

For each patient and for each AE, the following summary variables were then derived:

- A binary variable indicating at least one occurrence of the given AE over the course of the study for the given patients
- A categorical variable indicating the worst AE grade over the course of the study

Laboratory abnormalities associated with samples from C1D1 were graded in a manner consistent with CTCAE criteria, as follows: Albumin (Grade 1 : 3-3.5 g/dL; Grade 2: 2-<3 g/dL; Grade 3: < 2 g/dL); ALT and AST (Grade 1: 51-150 U/L, Grade 2: 151-250 U/L, Grade 3: 251-1000 U/L, Grade 4: >1000 U/L).

For each analyte and for each patient, the following summary variables were derived: A binary variable indicating the presence of at least one laboratory abnormality during Cycle 1; A categorical variable indicating the worst grade for the over the laboratory abnormality during Cycle 1.

The tagraxofusp exposure metrics to be evaluated in the analysis included the PopPK model predicted Cmax in the dosing interval on C1D1 and AUC0-24 following C1D1 dose. AUC0-24 was evaluated as a continuous measure, however for graphical and model diagnostic purposes only, AUC0-24 was divided in three bins (0-25 / 25-100 / > 100 µg.h/L). Associations between incidence and AUC0-24 were quantified via multiple-predictor logistic regression models. Candidate covariates evaluated for AE and laboratory abnormality models were disease status, baseline albumin, ALT and AST, presence or absence of quantifiable SL-401 during Cycle 3 or 4, presence or absence of Nab.

All the 6 analysed AEs exhibited both increasing incidence and increasing severity in association with both C1DA AUC0-24 and Cmax.

On the basis of the multiple-predictor logistic regression model as shown in Table 30, C1D1 AUC0-24 was estimated to increase significantly the odds of:

- Hypoalbuminemia laboratory abnormality by approximately 5.5x per 100 µg.h/L
- CLS AE by approximately 1.97x per 100 µg.h/L

- Elevated AST laboratory abnormality by approximately 227.1x per 100 µg.h/L

Table 30. Estimated effects of C1D1 AUc0-24 for AE and laboratory abnormalities

Adverse Event	Odds Ratio Per 100 µg•h/L Free Tagraxofusp AUC_{0-24}	95% CI
Hypoalbuminaemia AE	2.22	(0.62, 4.92)
Hypoalbuminaemia laboratory abnormality	5.05	(1.95, 23.28)
CLS AE	1.97	(1.24, 3.23)
Transaminase elevation AE	1.40	(0.87, 2.37)
Elevated ALT laboratory abnormality	4.96	(0.67, 605.86)
Elevated AST laboratory abnormality	227.10	(7.88, 22565)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24h; CI = confidence interval; CLS = capillary leak syndrome.
Source: Metrum Report STM0108F, Tables 12, 20, 25, 30, 36, and 43.

Quantifiable tagraxofusp in Cycle 3 was generally associated with increased risk of AEs and laboratory abnormalities. Quantifiable free tagraxofusp in Cycle 3 was evaluated as a potential covariate as an "indirect" way of possibly characterizing something different about patients with quantifiable concentrations in Cycle 3 versus patients who do not have quantifiable concentrations in Cycle 3. The Cycle 3 quantifiable exposure assessment was not intended to suggest that exposures occurring after the adverse event are 'causing' the adverse event but to indicate there may be other contributing factors that are correlated with quantifiable free tagraxofusp in Cycle 3. Presence of neutralizing ADA in Cycle 1 was associated with decreased risk for analysed laboratory abnormalities except albumin and for analysed AEs except CLS, for which the covariate was not found to be predictive.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology data are supported by 4 clinical studies in adult patients with haematological malignancies, including BPDCN where Study 0114 is the pivotal study.

Pharmacokinetics

Pharmacokinetic data of tagraxofusp are predominantly reported descriptively for two reasons: only free tagraxofusp was measured resulting in a high variability caused by anti-drug antibodies; due to an apparent disconnection of exposure to efficacy data.

Full PK sampling has been performed at several occasions. No dedicated clinical pharmacology studies in healthy subjects or in patients were conducted. No evaluations of tagraxofusp pharmacology in human biomaterials were performed.

Generally, based on the validation reports, the used bioanalytical methods developed for the detection and quantification of SL-401 and hIL3 ADA or Nab in human biological matrix comply with acceptance criteria. However for the quantification of the free tagraxofusp, the developed bioanalytical method suffers from the lack of selectivity. Since the calibration curve (in Beagle plasma), the QCs, and the method validation for selectivity (both in selected human low ADA plasma) were run with plasma that is not representative of the target population with regards to its ADA titers, this questions the reliability of the assay and the derived PK parameters, especially for low tagraxofusp concentrations. The sole

exception is the case where the ADA status is negative, where the method can be considered adequate. Therefore, the characterization of the tagraxofusp PK is considered adequately performed only in 4 or 5 patients depending on the PK parameter measured. Consequently, all the PK and PK/PD results could not be considered reliable.

The applicant was advised to provide a fully validated method of quantification of free tagraxofusp (fulfilment of the selectivity requirement) representative of the samples measured, however, the issues identified in the application prevent a recommendation to grant a marketing authorisation. Tagraxofusp is given as an intravenous infusion therefore no specific study of absorption is requested. Two formulations were used during the clinical development (a frozen liquid formulation or a lyophilized powder formulation), the patients with BPDCN in stage 4 of the study were treated with the lyophilized powder.

Due to the near ubiquitous immunization against diphtheria, it was expected that most of the patients have pre-existing ADA which have a clear impact on tagraxofusp PK. Indeed, only in 5 patients which were ADA negative at baseline, estimated distribution volume was 5.1 L suggesting that tagraxofusp is not distributed beyond the plasma and extracellular fluids, estimated clearance was 7.16 L/h with a short half-life of 0.714h. In patients who were ADA positive at baseline, distribution volume and clearance increased by a 4-fold and 1.7-fold respectively.

Since tagraxofusp is a recombinant protein, it could be considered to be degraded into amino-acids.

Dose proportionality could not be formally demonstrated and time dependency is expected and mediated by the time-dependent production of ADA. Inherent to the analytics of only free tagraxofusp, the PK is strongly dependent on ADA titers and thus very variable not only between subjects, but also between administration days and cycles. The population PK analysis based on this data reflects this variability and followingly has a poor performance and cannot be relied on. The same is true for the PK/PD analysis.

Due to the nature of the compound, a fusion protein, several studies are not required, such as renal and hepatic impairment studies, as well as age, gender or race dependence, given that the protein is expected to be degraded by proteolysis, which does not depend on organ function nor age.

Results of the NCA based analysis, even though they should be viewed with caution since the developed bioanalysis method for free tagraxofusp suffers from a lack of selectivity, do not contradict the assumption that renal and hepatic clearance, age, gender, race and weight have no effect on PK parameters.

Pharmacodynamics

Numerous toxins have been utilised as targeted toxins mainly linked to antibody or antibody fragments. Two very important toxins are Diphtheria toxin (DT) and Pseudomonas exotoxin (PE). Because these act catalytically they are highly potent, so one molecule gaining entry into the cytosol is sufficient to kill the cell. In the case of PE, it has been calculated that fewer than 1000 molecules of immunotoxin/cell is sufficient to cause complete tumour regressions (Kreitman and Pastan, 1998).

The proposed mechanism of action (MoA) of tagraxofusp is specific binding through CD123, translocation of the catalytic subunit to arrest protein synthesis, following internalisation of the diphtheria toxin. To support the postulated MoA, the applicant has suggested peripheral blood neutrophil count and bone marrow blast cells as PD endpoints, in addition to modelling approaches on both. However, the proposed MoA of tagraxofusp is not clear cut, especially in light of the heavy load of neutralising specific antibodies present. Observed trends in PD end-points (e.g., decrease in bone marrow blasts), might indicate a mechanistic explanation of targeted binding on blasts cells prior to apoptosis, but due to the total ADA load in 100% of patients, where 96% of patients had neutralising

antibodies, an adjuvant mechanism with a general stimulation of the immune system also appears as a probable scenario. The applicant has given a comprehensive and thorough discussion on potential mechanisms of action through which tagraxofusp may exert its effect on dendritic cancer cells in either free or bound form, highlighting the dynamic and multifaceted effect of ADAs and NAbs on the MoA of tagraxofusp. This was accepted by the CHMP.

As outlined above, exposure measurements are deemed unreliable and should therefore not be used for any E-R relationship considerations.

Detectable concentrations of free tagraxcofusp may not entirely represent its therapeutic effect, as target-bound tagraxofusp may still be available and biologically active in concentrations sufficient to maintain subject responses. Total concentrations of tagraxofusp (free and target bound), which according to the applicant, were unavailable, could be more closely related to the PD response.

According to literature (Feuillard et al., Blood 2002), most patients with BPDCN have skin lesions at diagnosis and subsequent or simultaneous involvement of the bone marrow, peripheral blood, and lymph nodes. The proposed PD end-point of bone marrow blasts, therefore, may not be optimal to reflect responses in all patients with BPDCN. In the 0114 study, the bone marrow is only affected by blastic dendritic cells in 50% of patients at baseline. Blast cells may apparently circulate in peripheral blood, confusing the picture even further. Bone marrow blast cell levels is not a part of the diagnostic tool for identification of BPDCN according to the WHO 2016 reclassification (Blood, 2016). Since bone marrow blast frequencies range from 0-94% in patients with BPDCN, and no correlation between bone marrow blast levels and clinical response to tagraxofusp were seen, the utility of monitoring BMBC as a PD marker of response is considered very low.

An appropriate ECG monitoring is expected for all compounds, including therapeutic proteins. Due to their size, it is unlikely that large fusion proteins like tagraxofusp, with a potential high specificity for their target antigens, would directly inhibit ion channels, i.e. hERG, responsible for cardiac repolarisation. However, if the drug has primary or secondary effects on cardiac function, it is plausible that the agent may alter dynamics of heart repolarisation, leading to QT prolongation. In the current analysis of QT, time-matched measurements of tagraxofusp concentration and collection of ECG data seem to be adequately performed, even if PK or ECG observations were missing from some patients. ECG measurements and modelling analyses indicated that tagraxofusp is not associated with a concentration-dependent prolongation of the QTcF interval. However, the observation that a considerable number of patients in the safety population is experiencing QT prolongation (see Clinical safety), may indicate a correlation between administration of tagraxofusp and cardiac repolarisation.

2.4.5. Conclusions on clinical pharmacology

Overall Tagraxofusp PK is highly impacted by ADA effect (pre-existing or treatment induced), which considerably affects tagraxofusp PK characterisation. At this stage, given the lack of selectivity of the developed bioanalytical method for the quantification of free tagraxofusp, the PK characterisation of tagraxofusp is considered adequately performed only in 4 or 5 ADA negative patients. Consequently, the applicant was advised to provide a fully validated method of quantification of free tagraxofusp (fulfilment of the selectivity requirement) representative of the samples measured (in particular with respect to the expected ADA levels in the target population). The proposed dosing rationale could be considered reasonable since efficacy has been observed beyond cycle 1. However, the issues identified in the application prevent a recommendation to grant a marketing authorisation.

The proposed mechanism of action (MoA) of tagraxofusp via a specific binding through CD123 and subsequent arrest in protein synthesis is still not fully elucidated, nonetheless the discussion provided by the applicant is considered acceptable.

2.5. Clinical efficacy

The primary efficacy data of tagraxofusp in patients with BPDCN are derived from Study STML-401-0114 which was initiated based on preliminary evidence from Study 50047.

2.5.1. Dose response studies

The dose response studies that were performed to support the dose selection for Tagraxofusp are Study 50047 and Study STML-401-0114.

Study 50047

The first in human clinical study of tagraxofusp was an investigator-sponsored study (Study 50047) in which 2 dosing regimens were evaluated. Regimen A consisted of doses every other day for up to 6 doses and required patients to be hospitalised during the 2-week dosing period. Five dose levels (4, 5, 7.07, 9.3, and 12.5 µg/kg/day) administered intravenously as a 15-minute infusion were evaluated. Dose-limiting toxicity was not reached during the dose escalation due to transient Grade 3 transaminase elevations which precluded the final 1 or 2 infusions, and patient unwillingness to undergo treatment for 2 weeks in the hospital. The schedule was changed to daily administration for 5 days (Regimen B) to improve drug delivery and patient compliance, as patients were hospitalised for 1 week rather than 2 weeks. Doses evaluated in the 5-day regimen ranged from 7.07 to 22.1 µg/kg/day. The MTD of tagraxofusp when administered as a single cycle consisting of daily × 5 doses was determined to be 16.6 µg/kg/day. Dose-limiting toxicities at the highest dose of 22.1 µg/kg/day included transient transaminase elevations and manifestations of capillary leak syndrome (CLS) (Frankel, 2014). Based on the totality of the data, the 12.5 µg/kg/day was identified as the RP2D based on a favourable risk/benefit profile, with a low incidence of adverse reactions and multiple major tumour responses after a single cycle of therapy.

Study STML-401-0114

Stage 1: Dose Escalation cohort

The purpose of Study STML-401-0114 was to confirm the previous Phase 1/2 experience with SL-401 in Study 50047, in which a single cycle of SL-401 was administered to patients with hematologic malignancies, including AML, R/R AML, or BPDCN. Study 0114 was intended to generate clinical experience with multiple cycles of SL-401 to identify the optimal dose for BPDCN and AML patients, and to evaluate the potential clinical benefit of a multi-cycle regimen, with up to 6 cycles initially planned. The primary objective of Stage 1 of the study was to determine the MTD, or the MTeD, where multiple DLTs were not observed.

The design of Stage 1 followed a standard 3+3 design to assess ascending doses of SL-401 administered on a daily × 5 schedule every 21 days. Approximately 9 to 18 patients were planned to be treated at doses of 7, 9, 12, or 16 µg/kg/day. (The 16 µg/kg/day dose was evaluated only in patients with AML.) The MTD was defined as the highest dose level where less than 2/3 or 2/6 patients experienced a DLT. No intrapatient dose escalation was allowed. Tumor response was assessed according to sites of disease involvement (including BM, blood, skin, lymph nodes, and visceral organs).

Upon completion of Stage 1 and analysis of the dose escalation results, the MTD was determined to be 16 µg/kg/day in patients with AML; this dose was not tested in patients with BPDCN, based in the observed responses in terms of CR duration as the 12 µg/kg/day dose in this patient population.

Stage 2: Expansion cohort

Stage 2 of Study STML-401-0114 included 2 expansion cohorts at the dose identified in Stage 1: 1 cohort for 40 to 50 patients with first-line and R/R BPDCN and 1 for 36 patients with AML. An active control arm was not included. The purpose of the expansion stage (Stage 2) was to evaluate efficacy assessed by ORR, and further characterize the safety profile of multi-cycle therapy with SL-401 at the RP2D, 12 µg/kg administered intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle.

2.5.2. Main study

STML-401-0114

Methods

Study 0114 was a non-randomized, open-label, single-arm, multicenter study of SL-401 in BPDCN and AML patients divided into 4 stages. Each study stage represents a distinct development phase, with Stage 1 results supporting the findings from the previous study 50047 and Stage 2 results providing the preliminary evidence of efficacy. Combined, Stages 1-2 provided the basis for the design of Stage 3 (the pivotal cohort) in patients with first-line BPDCN. At the time of submission Stage 4 was still ongoing, the study was concluded in early 2020.

Study Participants

The inclusion/exclusion criteria for patients with BPDCN, tagraxofusp dose and treatment schedule are the same across Stages 2-4, with the exception that only first-line BPDCN patients are eligible for Stage 3 (as of Amendment 9). Patients meeting the following criteria were eligible for enrolment (only inclusion criteria relevant to the BPDCN diagnosis are included in the list):

Inclusion criteria

1. The patient had a diagnosis of BPDCN (Protocol Stages 1-4) according to WHO confirmed by hematopathology (BPDCN) (Facchetti, 2008).
2. The patient had histological and/or cytological evidence of BPDCN by pathologic assessment at the investigative site according to WHO classification (Facchetti, 2008) by a pathologist with expertise in hematologic malignancies, that could be measured for treatment response and was either:
    - Previously untreated (i.e., first-line) (Protocol Stages 2-4).
    - Persistent or recurrent in the peripheral blood, BM, spleen, lymph nodes, skin, or other sites after previous treatment with at least 1 line of systemic therapy for BPDCN, eg, SCT or chemotherapy (Protocol Stages 1, 2, and 4). A pathology specimen was required to be available for central pathology review for all BPDCN patients enrolled in Protocol Stages 2-4.
3. The patient was ≥18 years old.
4. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.

5. The patient had adequate baseline organ function, including cardiac, renal, and hepatic function:
    - Left ventricular ejection fraction (LVEF) ≥ the institutional lower limit of normal as measured by multigated acquisition (MUGA) scan or 2-dimensional echocardiography within 28 days before start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG).
    - Serum creatinine ≤1.5 mg/dL (133 µmol/L).
    - Serum albumin ≥3.2 g/dL (32 g/L) (albumin infusions were not permitted in order to enable eligibility).
    - Bilirubin ≤1.5 mg/dL (26 µmol/L).
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal (ULN).
6. If the patient was a woman of child-bearing potential (WOCBP), she had a negative serum or urine pregnancy test within 1 week before treatment.
7. The patient signed informed consent before initiation of any study-specific procedures or treatment.
8. The patient was able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.
9. The patient (male and female) agreed to use acceptable contraceptive methods for the duration of time on the study, and to continue to use acceptable contraceptive methods for 2 months after the last infusion of tagraxofusp.

Exclusion criteria

1. The patient had persistent clinically significant toxicities ≥Grade 2 from previous chemotherapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]).
2. The patient received treatment with chemotherapy, wide-field radiation, or biologic therapy within 14 days of study entry.
3. The patient received treatment with another investigational agent within 14 days of study entry.
4. The patient previously received treatment with tagraxofusp.
5. The patient had an active malignancy and/or cancer history (excluding AML, BPDCN, or antecedent MDS) that may have confounded the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) with substantial potential or recurrence and/or ongoing active malignancy were required to be discussed with the Sponsor before study entry. Patients with the following neoplastic diagnoses were eligible: nonmelanoma skin cancer, carcinoma in situ, cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
6. The patient had clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months before study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).

7. The patient had uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the Investigator would have put the patient at significant risk for pulmonary complications during the study.
8. The patient had known active or suspected central nervous system (CNS) leukaemia. If suspected, CNS leukaemia was required to be ruled out with relevant imaging and/or examination of cerebrospinal fluid.
9. The patient was receiving immunosuppressive therapy, with the exception of low-dose prednisone (≤10 mg/day), for treatment or prophylaxis of graft-versus-host disease (GVHD). If the patient had been on immunosuppressive treatment or prophylaxis for GVHD, the treatment(s) must have been discontinued at least 14 days before study treatment and there must have been no evidence of ≥Grade 2 GVHD.
10. The patient had uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would have limited compliance with study requirements.
11. The patient was pregnant or breast feeding.
12. The patient had known positive status for human immunodeficiency virus or active or chronic Hepatitis B or Hepatitis C.

Treatments

The populations included in each stage were as follows:

- **Stage 1:** Patients with first-line or R/R BPDCN and AML.
- **Stage 2:** Patients with first-line or R/R BPDCN and AML.
- **Stage 3** (Pivotal Cohort): Patients with first-line BPDCN only.
- **Stage 4:** Patients with first-line or R/R BPDCN.

Two pharmaceutical forms of SL-401 have been tested in the Study 0114; SL-401 solution and SL-401 Lyophilized Powder. SL-401 is a non-preserved, sterile, liquid dosage form intended for IV infusion containing an aqueous solution of 1.0 mg of SL-401. SL-401 Lyophilized Powder is a non-preserved, sterile lyophilized white powder and is supplied in a single-use vial containing 1.0 mg of SL-401. It is intended for IV infusion only after reconstitution followed by further dilution with 0.9% Sodium Chloride, USP.

In all study stages, SL-401 was administered as a daily intravenous (IV) infusion over 15 minutes for up to 5 consecutive days of a 21-day cycle, initially for up to 6 cycles, with the potential to receive additional cycles, with the approval of the Medical Monitor. By Amendment 8 (08 Feb 2016), it was stipulated that patients who benefitted from treatment, in the judgment of the Investigator, may have received repeated cycles of SL-401; no maximum duration of therapy was set.

In Stage 1, patients were assigned to a dose cohort according to the dose-escalation scheme. In Stages 2 to 4, all patients received SL-401 at a dose RP2D identified in Stage 1 (i.e., 12 µg/kg/day).

Patients received the following premedication approximately 60 minutes before each SL-401 infusion:

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

- Ranitidine 50 mg IV (or an equivalent dosage of another H2-histamine antagonist)

The first cycle of SL-401 was administered in the inpatient setting, with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending approximately 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 were administered in the inpatient setting or in a suitable outpatient ambulatory care setting that was equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, at the discretion of the Investigator and according to institutional guidelines and capabilities. Patients were monitored for at least 4 hours following the administration of each infusion of SL-401.

Objectives

Primary Objectives

- **Stage 1:** To determine the maximum tolerated dose (MTD), or the maximum tested dose (MTeD) where multiple DLTs were not observed, of SL-401.
- **Stage 2:**
    - To determine the efficacy of SL-401 in BPDCN patients, as assessed by objective response rate (ORR).
    - To characterize the safety profile of SL-401 at the MTD or MTeD in both patients with AML and BPDCN.
- **Stage 3:**
    - To determine the CR rate (i.e., CR+ complete response with minimal residual skin abnormality [CRc]) in patients with first-line BPDCN.
    - To characterize the safety profile of SL-401 in patients with first-line BPDCN.
- **Stage 4:**
    - Further characterize the efficacy of tagraxofusp in first-line and R/R patients with BPDCN following the completion of Stage 2 and Stage 3, respectively, as assessed by the rate of CR (CR + CRi + CRc).
    - Further characterize the safety profile of tagraxofusp among first-line and R/R patients with BPDCN.
    - Characterize the efficacy and safety of a lyophilized formulation of tagraxofusp among R/R and first-line patients with BPDCN.

Secondary Objectives

The secondary objectives were to:

- Determine the CR rate (i.e., CR + complete response with minimal residual skin abnormality [CRc]) for Stage 1 and Stage 2, and ORR for Stage 3 patients.
- Estimate DOR, progression-free survival (PFS), and OS in BPDCN patients.
- Enable preliminary characterization of the estimated ORR in patients with relapsed/refractory (R/R) AML, including in subsets of patients with R/R AML based on pretreatment blast count, cytogenetics, or CD123 measurement.
- Estimate DOR, PFS, and OS in patients with AML.
- Characterize the pharmacokinetic (PK) and immunogenicity of SL-401.

Outcomes/endpoints

Endpoints and definitions are presented in Table 31 and Table 32. Response criteria are presented in Table 33.

Table 31. Primary and key secondary efficacy endpoints

Endpoint	Definition
Primary Endpoint	
CR rate	CR+CRc
Secondary Endpoints	
Key secondary endpoint: Duration of CR	Among patients with CR or CRc, the time from when the criteria were first met for CR/CRc (whichever was recorded first) until the date the criteria for relapse after CR/CRc were met. This could have been the occurrence of PD or relapse. In the case that PR or SD followed CR/CRc and there was no evidence that response rebounded to CR/CRc, duration of CR ended at the time of first reduction of response to below CR/CRc. If CRi followed CR/CRc, it was not considered evidence of relapse. For patients who received SCT after CR/CRc, duration of CR included time to disease relapse post-transplant. Patients who were lost to follow-up or who did not relapse after CR/CRc as of the cutoff for analysis were censored on the latter of the date of last treatment with tagraxofusp or date of last disease assessment recorded prior to the analysis cutoff date.
OS	Time from the date of first infusion of tagraxofusp to the date of death from any cause. Patients alive or lost to follow-up were censored on the last date known to be alive before the analysis cutoff date.
ORR	Rate of CR (CR+CRc), CRi, or PR after treatment.
DOR	Among patients with a CR, CRc, CRi, or PR, the time from when the response criteria were first met until the date the criteria for relapse (including SD, PD, or relapse) after CR/CRc/CRi/PR were met. For patients who received SCT after CR/CRc/CRi/PR, DOR included time to disease relapse post-transplant. Patients who were lost to follow-up or who did not relapse after objective response as of the cut-off for analysis were censored on the latter of the date of last treatment with tagraxofusp or date of last disease assessment recorded prior to the analysis cut-off date.
PFS	Among all patients, the time from the date of first infusion of tagraxofusp to the date of PD or death from any cause.

Abbreviations: CR = complete response; CRc = complete response with minimal residual skin abnormality; CRi = complete response with incomplete blood count recovery; DOR = duration ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RFS = relapse-free survival; SCT = stem cell transplant; SD = stable disease.

Table 32. Study 0114: Key Exploratory Efficacy Endpoints

Endpoint	Definition
Time-to-event endpoints	Time to CR (TTCR): Among patients with CR or CRc, time from initiation of treatment with tagraxofusp to CR (CR or CRc, whichever is achieved first).
	Time to response (TTR): Among patients with CR, CRc, CRi, or PR, time from initiation of treatment with tagraxofusp to CR, CRc, CRi, or PR, whichever occurs first.
	Relapse-free survival (RFS): Among patients with CR/CRc, time from CR or CRc to disease progression or death.
Bridge to SCT	The number and proportion of patients who receive a SCT subsequent to achieving an Investigator-determined outcome from tagraxofusp that is deemed by the Investigator to enable a SCT.

Abbreviations: CR = complete response; CRc = complete response with minimal residual skin abnormality; CRi = complete response with incomplete blood count recovery; PR = partial response; SCT = stem cell transplant.

Table 33. Overall tumour response criteria for BPDCN patients

Response	Location	Criteria
CR	Marrow[1]	Normalisation of blast percentage (≤5%) [1]
	Peripheral Blood	Normalisation of neutrophil count (≥1,000/µL) and platelet count (≥100,000/µL) Absence of leukaemic blasts
	Skin[2]	100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[2]
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared
CRi	Marrow[1]	Normalisation of blast percentage (≤5%)[1]
	Peripheral Blood	Incomplete recovery of neutrophil and/or platelet count. Absence of leukemic blasts
	Skin[2]	100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[2]
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared
CRc	Marrow[1]	Normalisation of blast percentage (≤5%)[1]
	Peripheral Blood	Normalisation of neutrophil count (≥1,000/µL) and platelet count (≥100,000/µL) Absence of leukemic blasts
	Skin[2]	Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)[2]
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared
PR	Marrow[1]	Decrease by ≥50% in blast percentage to 5 – 25%[1]
	Peripheral Blood	Normalisation of neutrophil count (≥1,000/µL) and platelet count (≥100,000/µL)
	Skin[2]	50% – <100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[2]
	Nodal Masses	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes
	Spleen, Liver	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen
SD		Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks

Response	Location	Criteria
Relapse after CR/CRi/CRc	Marrow[1]	Blast percentage >5% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)[1]
	Peripheral Blood	Presence of leukemic blasts
	Skin[2]	Increase in skin score greater than the sum of nadir plus 50% baseline score[2]
	Nodal Masses	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than 1 node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	>50% increase from nadir in the SPD of any previous lesions
Relapse after PR	Marrow[1]	Blast percentage ≥25% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)[1]
	Skin[2]	Increase in skin score greater than the sum of nadir plus 50% baseline score[2]
	Nodal Masses	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than 1 node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	>50% increase from nadir in the SPD of any previous lesions
PD	Marrow[1]	≥50% increase in blasts from baseline (and blast percentage >5%)[1]
	Peripheral Blood	One or more of the following: • ≥50% decrease from peak remission levels in platelets or granulocytes • Reduction in haemoglobin concentration by at least 2 g/dL • Transfusion dependence
	Skin[2]	One or more of the following: • ≥25% increase in skin disease from baseline[2] • Any new tumours in patients without tumours at baseline
	Nodal Masses	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than 1 node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	>50% increase from nadir in the SPD of any previous lesions

Abbreviations: BM = bone marrow; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = complete response with minimal residual skin abnormality; CRi = complete response with incomplete blood count recovery; CT = computed tomography; mSWAT = Modified Severity Weighted Assessment Tool; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of the product of the diameters.
Note: All parameters detailed above (including BM, blood, skin [including mSWAT quantification], lymph nodes and viscera) were assessed both at baseline and stipulated subsequent time points. Responses were determined via comparison to baseline values (or post-treatment nadir values as stipulated in the above table).
[1]In settings in which there was a change in the blast population on BM evaluation by means of flow cytometry or other molecular methodology without a similar degree of change in the morphologic blast percentage, the morphologic percentage was utilized to determine response/progression.
[2]The percentage of clearance or increase in skin disease was calculated using the mSWAT

Sample size

The sample size was originally planned to be approximately 40 to 50 BPDCN patients, including approximately 40 previously treatment-naïve patients treated with the SL-401 the tagraxofusp RP2D (12 µg/kg/day), with the analysis of ORR to be used to determine the efficacy of SL-401 in patients with first-line and R/R BPDCN.

Stage 3 was a separate prospective cohort designed to confirm the efficacy of tagraxofusp in patients with first-line BPDCN observed in Stages 1 and 2. The sample size allocated for Stage 3 was intended to

satisfy specific statistical criteria. The primary efficacy analysis for Stage 3 would compare the lower bound of a 2-sided 95% Clopper-Exact confidence interval (CI) containing the true CR rate to a rate of 10%. Statistical significance would be determined if the lower bound of this CI fell above 10%. Assuming a CR rate of at least 60%, a minimal sample size of 10 first-line BPDCN patients provided at least 90% power for the primary efficacy assessment. To be evaluable for efficacy, the BPDCN modified intent-to-treat (mITT) population required central pathology review to confirm the diagnosis. As central review could not be performed in real time and a delay in confirmation of diagnosis may have occurred, a maximum of 15 patients were permitted to enroll during the enrolment period from 26 October 2016 to 17 March 2017 to ensure an adequate number of patients was available for analysis. To avoid possible selection bias, all first-line BPDCN patients enrolled in this time period were to be included in the Stage 3 analysis.

Randomisation

Study STML-401-0114 is a nonrandomized study.

Blinding (masking)

Study STML-401-0114 was an open-label study; no blinding methods were employed.

Statistical methods

The cutoff date for analysis of efficacy, safety, and immunogenicity data was 31 Jan 2018.

Analysis populations

The following patient populations were evaluated and used for presentation and analysis of the data:

- Modified Intent-to-Treat (mITT) Population: All patients who were eligible based on the Screening criteria and who received at least 1 dose of SL-401. For BPDCN patients to be eligible for mITT they must also have had a diagnosis of disease based on central pathology review of "Confirmed" or "Inconclusive: Likely BPDCN". Patients were grouped according to the planned dose level at time of enrollment. However, as no major protocol violations warranting exclusion from analysis were identified by the applicant, a per-protocol population was not defined and no analyses for this population were performed.
- Immunogenicity Population: All patients enrolled in the study who received at least 1 dose of SL-401 and had a baseline sample taken with reportable result for ADA or AIA. The immunogenicity population was used for summary of immunogenicity status pre-treatment. The Immunogenicity Evaluable Population included all patients enrolled in the study who received at least 1 dose of SL-401 and had a baseline sample and at least 1 sample taken after drug administration with reportable result for ADA or AIA.
- Safety Population, defined as all patients enrolled in the study who received at least 1 dose of SL-401. Patients were grouped according to the actual dose level received (see safety sections of the CHMP AR).

Primary and secondary endpoints

The consistency of the methodology (disease diagnosis, inclusion and exclusion criteria, response criteria, and schedule of assessments) across the conduct of the study enabled pooling by baseline disease state across stages. The pooling of data for efficacy analysis at 12 µg/kg/day is shown in Table 34.

Table 34. Pooling of Data for Efficacy Analysis at 12 µg/kg/day

Disease and Line of Therapy	First-Line BPDCN			R/R BPDCN		First-Line/ R/R AML
Patient Population	**mITT**			**mITT**		**mITT**
Stages Included	3	1&2	All	1&2	All	1&2
CR+Duration	X	X	X	X	X	
BMCR+Duration	X		X			
ORR+Duration	X	X	X	X	X	X
Percent SCT	X		X		X	X
PFS			X		X	
OS			X		X	X
TTCR	X		X		X	
TTR	X		X		X	
TT BMCR	X		X		X	
RFS	X		X		X	
TTP	X		X		X	

mITT = modified intent to treat population; BPDCN = blastic plasmacytoid dendritic cell neoplasm; R/R = relapsed/refractory; CR = complete response (CR+CRc); BMCR = bone marrow complete response; ORR = objective response rate; SCT = stem cell transplant; PFS = progression free survival; OS = overall survival; TTCR = time to complete response (CR+CRc); TTR = time to response (CR+CRi+CRc+PR); TT BMCR = time to bone marrow complete response; RFS = relapse free survival; TTP = time to progression.

The definitions of select key primary and secondary efficacy endpoints are summarised above. The primary efficacy endpoint of Study 0114 was tabulated as the number and percentage of patients who achieved CR+CRc. The 95% Clopper-Pearson Exact CIs around the rate of CR+CRc were presented. A formal statistical hypothesis test was performed for the primary efficacy endpoint, to test that the rate of CR+CRc in first-line patients in Stage 3 exceeds the lower benchmark of 10%.

Results

Participant flow

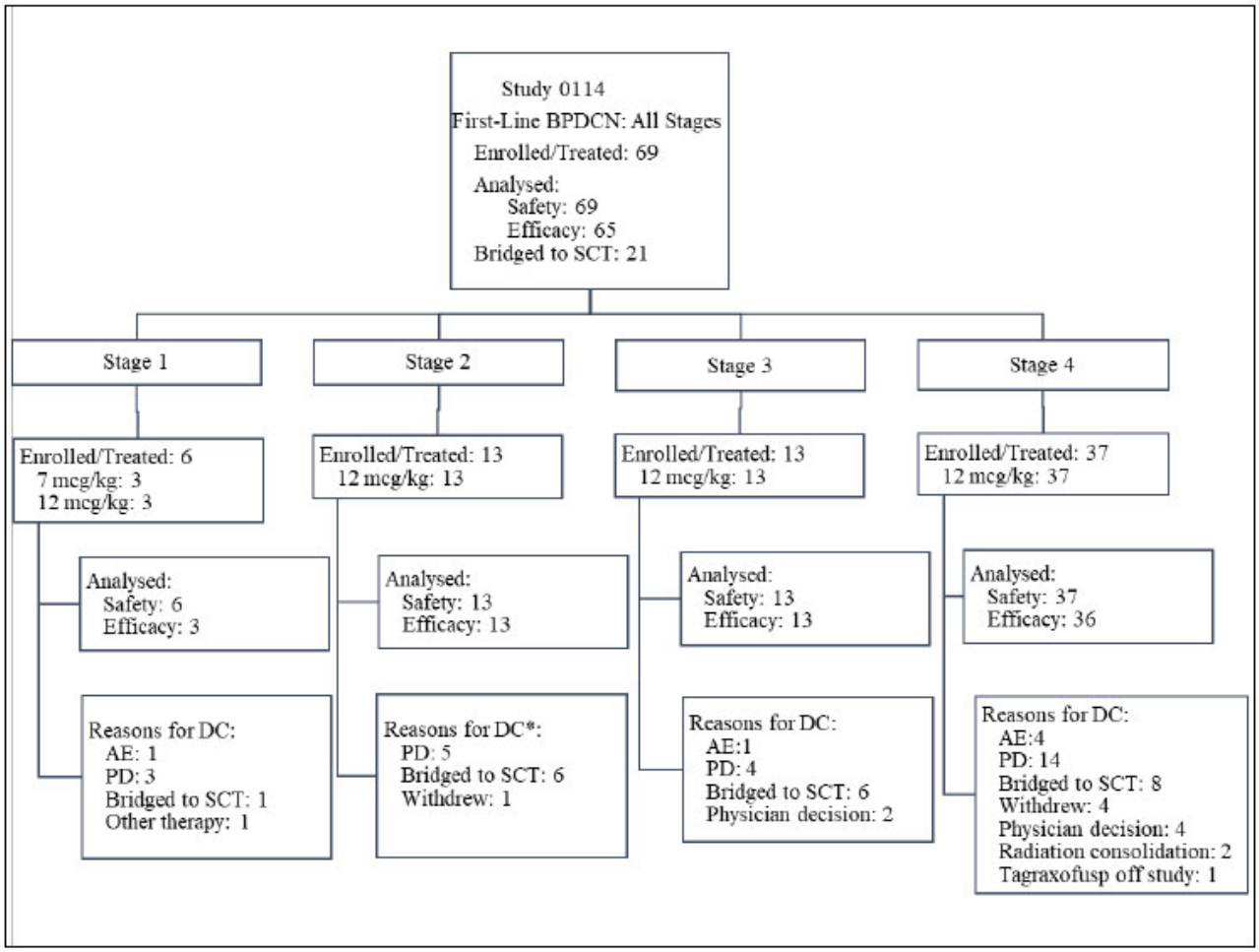


Figure 8. Participant flow First Line BPDCN

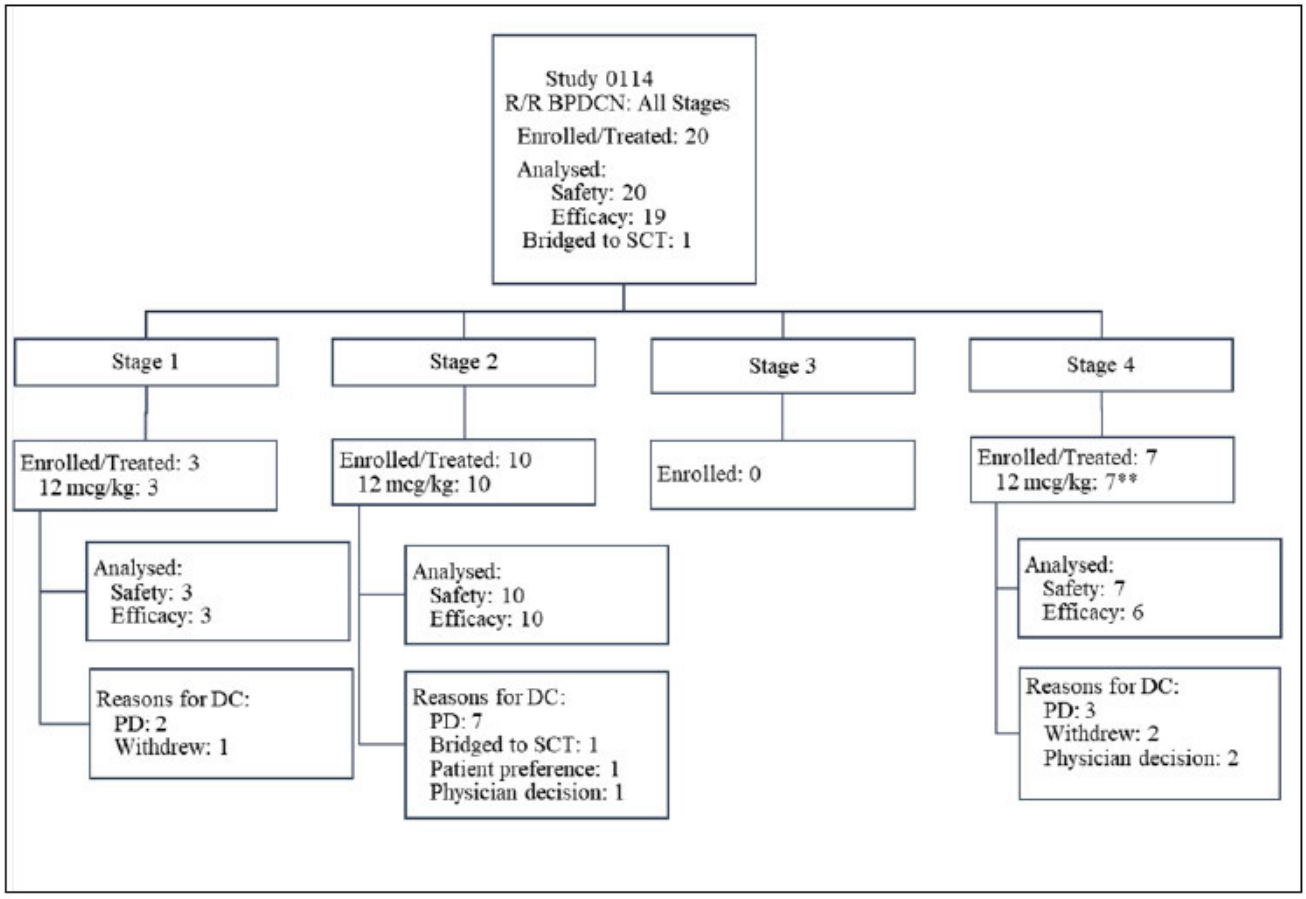


Figure 9. Participant flow R/R BPDCN

A summary of patient enrolment by disease, stage, and SL-401 dose is presented in Table 35. Patient disposition for first-line BPDCN patients, overall and by stage, is presented in Table 39. Median duration of exposure for all first-line BPDCN patients was 96 days (range 2 to 927 days). Disposition for R/R BPDCN patients, overall and by stage, is presented in Table 40. Median duration of exposure for all R/R BPDCN patients was 48 days (range 6 to 138 days).

In stage 4, 2 of 44 patients enrolled received the liquid formulation, they are added to the study results presented below. The study results from all stage 4 patients are given as supplement in the later section.

Table 35. Summary of enrolment by disease, stage and SL-401 dose, liquid formulation

Disease	Stage 1 N	Stage 2 N	Stage 3 N	Stage 4 N	Overall N
First-Line BPDCN					
7 µg/kg/day	3	0	0	0	3
12 µg/kg/day	3	13	13	0	29
Total	***6***	***13***	***13***	***0***	***32***
R/R BPDCN					
12 µg/kg/day	3	10	0	2	15
Total	***3***	***10***	***0***	***2***	***15***
AML					
7 µg/kg/day	3	0	0	0	3
9 µg/kg/day	3	0	0	0	3
12 µg/kg/day	2	34	0	0	36
16 µg/kg/day	6	1[1]	0	0	7
Total	***14***	***35***	***0***	***0***	**49**
Overall	**23**	**58**	**13**	**2**	**96**

Abbreviations: AML = Acute Myeloid Leukemia; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; R/R = Relapsed/Refractory.
1 One AML patient (06-018) was assigned to a dose of 12 µg/kg/day, but received 16 µg/kg/day.
Source: Table 14.1.1A, Table 14.1.1B, and Listing 16.2.5.1A.

Table 36. Patient enrolment and disposition: first-Line BPDCN, overall and by stages 1-3

Parameter	Stage 1 (N=6) n (%)	Stage 2 (N=13) n (%)	Stage 3 (N=13) n (%)	Overall (N=32) n (%)
Total Number of Patients:				
Treated	6 (100)	13 (100)	13 (100)	32 (100)
Ongoing on Treatment at Data Cutoff[1]	0	2 (15.4)	0	2 (6.3)
Study Populations:				
Modified Intent-to-Treat Population	6 (100)	13 (100)	13 (100)	32 (100)
Safety Population	6 (100)	13 (100)	13 (100)	32 (100)
Immunogenicity Population	6 (100)	13 (100)	13 (100)	32 (100)
Discontinued Study	6 (100)	11 (84.6)	13 (100)	30 (93.8)
Primary Reason for Discontinuation				
Disease Recurrence/ Progression	3 (50.0)	5 (38.5)	4 (30.8)	12 (37.5)
Physician Decision[2]	0	1 (7.7)	3 (23.1)	4 (12.5)
Adverse Event	1 (16.7)	0	1 (7.7)	2 (6.3)
Other[2]	2 (33.3)	5 (38.5)	5 (38.5)	12 (37.5)
Received SCT Since Discontinuation[3]				
Yes	2 (33.3)	8 (61.5)	9 (69.2)	19 (59.4)
Allogeneic	1 (16.7)	5 (38.5)	7 (53.8)	13 (40.6)
Autologous	1 (16.7)	2 (15.4)	0	3 (9.4)
RIC Allogeneic	0	0	2 (15.4)	2 (6.3)
Other	0	1 (7.7)	0	1 (3.1)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; RIC = Reduced Intensity Conditioning; SCT = Stem Cell Transplant.
1 31 Jan 2018.
2 Of the 12 patients discontinuing for "other" reasons, 11 had been/were being bridged to SCT and the remaining patient discontinued SL-401 to receive an alternate treatment. Two patients who were discontinued due to physician decision also were bridged to SCT (Listing 16.2.1.1).
3 Patients who reported any SCT after treatment with SL-401 were included (ie, including patients bridged to SCT [N=13] and those who had progression on study and then received subsequent SCT [N=6]).
Source: Table 14.1.1A.

Table 37. Patient enrolment and disposition: relapsed/refractory BPDCN, overall and by stage, liquid formulation

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

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

Recruitment

Study 0114 was initiated June 2014, and efficacy and safety data collected through January 2018 are from patients enrolled in or before 17 March 2017. Nine study centres in the United States (US) were included in this study, with patients enrolled at 7 of these 9 centres at the time of the original data cut-off of 31 January 2018. Patients enrolled in stage 3 started treatment between 16 Nov 2016 and 23 Feb 2017, and the cut-off for analysis was 31 Jan 2018. The study was ongoing as of 31 Jan 2018 (with Stage 4 open for enrolment at the time of the dossier submission).

Conduct of the study

Protocol amendments

Protocol Amendment 5 (28 Jul 2014) was the first protocol version under which patients were enrolled. There have been 4 amendments to the protocol since Protocol Amendment 5.

Protocol Amendment 6 (01 Dec 2014) was implemented during the Stage 1 dose-escalation phase with the following main changes:

- Provide risk mitigation strategies for the tagraxofusp related serious adverse reaction capillary leak syndrome (CLS):

- modification of the entrance criteria to require that patients have a normal LVEF before study entry
- more rigorous monitoring of patients during the infusion period in each cycle, including daily assessment of body weight.
- clarified that in the setting of early signs/symptoms consistent with CLS, including weight gain, hypotension, and/or decreased serum albumin, tagraxofusp treatment was to be delayed for a minimum of 1 day until there was evidence of stability of these signs/symptoms.

Protocol Amendment 7 (11 Aug 2015) was implemented with the enrolment of Stage 2 BPDCN patients and contained the following main changes:

- Incorporation of additional risk mitigation strategies for CLS including requirement of higher minimum serum albumin level for eligibility and cessation of therapy in a setting of significant albumin reductions or Grade 3 (or higher) transaminase elevations. Furthermore, in the setting of CLS signs or Grade 3 transaminase elevation, fewer than 5 doses of investigational therapy could have been administered in a given cycle.
- BPDCN diagnosis was to be made or confirmed by the pathology laboratories at the investigative sites; subsequent to enrolment, pathology material was to be submitted for central pathology review to confirm the BPDCN diagnosis.
- It was clarified that an IRC would assess response for BPDCN patients.
- The timing of and procedures for tumour response assessments in BPDCN patients were augmented, as follows:
  - A more detailed schedule for BM aspirate (± biopsy) subsequently to C2 was specified for patients enrolled in Stage 2.
  - The quantification of skin disease burden via the mSWAT instrument was required at the time of each skin assessment.

Protocol Amendment 8 (08 Feb 2016). The principal changes made by this amendment affected BPDCN patients in Stage 2, as follows:

- The entrance criteria were revised such that in addition to patients with R/R BPDCN, patients with previously untreated BPDCN would be eligible for enrollment.
- Study objectives for BPDCN patients enrolled in Stage 2 were revised to include the following:
  - Primary objective: Efficacy as assessed by ORR.
  - Secondary objective: CR rate (including CRi and CRc).
  - Secondary objective: Estimation of DOR, PFS, and OS.
- Clarifications were made regarding disease measurements and response assessment such that it was specifically stated that positive sites of disease identified during Screening were required to be followed during the study at every response evaluation.
  - Sites with no evidence of disease during Screening were to be documented as such and an assessment that baseline disease was not present needed to be adequately documented in source and recorded in the clinical database; thereafter, these sites of disease did not need to be followed, unless there was evidence of PD.
- It was clarified that patients would be followed for response and survival until assessment of the primary and secondary objectives was complete for all patients. Accordingly, patients in CR

or PR at the time of discontinuation of SL-401 were to continue to have disease assessments performed on an every 6-week basis (±1 week) through 6 months post-baseline, and then on an every 90-day basis or until, in the judgment of the Investigator, there was evidence of relapsed or progressive disease.

- The maximum duration of SL-401 therapy of 6 cycles was eliminated, and it was stipulated that patients could continue to receive SL-401 as long as they were benefitting from treatment, in the Investigator's opinion.

Protocol Amendment 9 (08 Feb 2017) implemented the outcome from a meeting with FDA to discuss an interim analysis of efficacy data from 32 BPDCN patients enrolled in Stages 1 and 2 between 06 Oct 2014, and 29 Aug 2016:

- Stage 2 of the study was closed.
- Stage 3 of the study was added. Any patient with first-line BPDCN enrolled on or after 26 Oct 2016, was included in Stage 3 until a sufficient number of patients were enrolled to ensure 10 patients were included in the mITT analysis population. The primary endpoint for this cohort was the CR rate.
- Stage 4 of the study was added, into which any patients with R/R BPDCN enrolled on or after 26 Oct 2016, were to be allocated. Furthermore, after the maximum number of planned first-line BPDCN patients were enrolled in Stage 3, any additional first-line BPDCN patients were to be enrolled in Stage 4. It was planned that BPDCN patients enrolled in Stage 4 subsequent to completion of enrollment in Stage 3 may have received a lyophilized formulation of tagraxofusp for injection.
- Based on these changes, the total study sample size was increased to up to 120 patients (including ~70 BPDCN patients)

Baseline data

Baseline demographics for first-line BPDCN are presented in Table 38. Baseline demographics for relapsed/refractory BCPN are given in Table 39. Baseline disease characteristics for first-line BPDCN are presented in Table 40. Baseline disease characteristics for relapsed/refractory BCPN are given in Table 41.

Table 38. Demographic and Baseline Characteristics: First-Line BPDCN, Overall and by Stage (mITT Population)

	Stage			
Parameter / Statistic	**1 (N=6)**	**2 (N=13)**	**3 (N=13)**	**Overall (N=32)**
Gender, n (%)				
Male	5 (83.3)	10 (76.9)	11 (84.6)	26 (81.3)
Female	1 (16.7)	3 (23.1)	2 (15.4)	6 (18.8)
Race, n (%)				
White	5 (83.3)	12 (92.3)	13 (100)	30 (93.8)
American Indian or Alaska Native	1 (16.7)	0	0	1 (3.1)
Other	0	1 (7.7)	0	1 (3.1)
ECOG Performance Status, n (%)				
0	3 (50.0)	6 (46.2)	8 (61.5)	17 (53.1)
1	3 (50.0)	7 (53.8)	5 (38.5)	15 (46.9)
Age (year)				
N	6	13	13	32
Mean (StD)	67.0 (10.49)	62.5 (17.72)	61.7 (17.15)	63.0 (16.04)
Median	64	69	65	67.5
Minimum, Maximum	54, 82	28, 84	22, 84	22, 84
Height (cm)				
N	5	12	13	30
Mean (StD)	173.4 (7.02)	171.6 (10.88)	176.2 (8.19)	173.9 (9.17)
Median	175	171	178	174.5
Minimum, Maximum	163, 182	154, 190	163, 188	154, 190
Weight (kg)				
N	6	13	13	32
Mean (standard deviation)	92.48 (6.299)	92.35 (16.190)	89.46 (17.674)	91.20 (15.196)
Median	92	86.8	83.8	86.8
Minimum, Maximum	85.5, 101.9	63.4, 116.0	69.3, 128.2	63.4, 128.2

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; ECOG = Eastern Cooperative Oncology Group; mITT= modified Intent-to-Treat; StD = Standard Deviation.

Table 39. Demographic and Baseline Characteristics: Relapsed/Refractory BPDCN, Overall and by Stage (mITT Population)

Parameter / Statistic	Stage 1 (N=3)	Stage 2 (N=10)	Stage 4 (N=2)	Overall (N=15)
Gender, n (%)				
Male	3 (100)	8 (80.0)	2 (100)	13 (86.7)
Female	0	2 (20.0)	0	2 (13.3)
Race, n (%)				
Asian	1 (33.3)	0	1 (50.0)	2 (13.3)
White	2 (66.7)	10 (100)	1 (50.0)	13 (86.7)
Other	0	0	0	0
ECOG[1]				
0	1 (33.3)	4 (40.0)	0	5 (33.3)
1	2 (66.7)	6 (60.0)	2 (100)	10 (66.7)
Age (year)				
N	3	10	2	15
Mean (StD)	72.0 (7.94)	69.7 (9.31)	61.0 (24.04)	69.0 (10.84)
Median	75	72	61	72
Minimum, Maximum	63, 78	54, 80	44, 78	44, 80
Height (cm)				
N	3	9	2	14
Mean (StD)	168.0 (7.81)	167.6 (8.68)	170.5 (10.61)	168.1 (8.09)
Median	164	166	170.5	165
Minimum, Maximum	163, 177	156, 178	163, 178	156, 178
Weight (kg)				
N	3	10	2	15
Mean (StD)	67.23 (4.966)	79.62 (9.731)	80.85 (21.284)	77.31 (11.141)
Median	70	81.4	80.85	79.6
Minimum, Maximum	61.5, 70.2	61.7, 96.0	65.8, 95.9	61.5, 96.0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; mITT = modified Intent-to-Treat; StD = Standard Deviation.

Table 40. Primary Disease Characteristics: First-Line BPDCN Patients, Overall and by Stage (mITT Population)

Parameter / Statistic	Stage 1 (N=6)	Stage 2 (N=13)	Stage 3 (N=13)	Overall (N=32)
Time Since BPDCN Diagnosis (months)[1]				
N	6	13	13	32
Mean (StD)	2.89 (3.743)	1.70 (1.257)	1.03 (0.883)	1.65 (1.905)
Median	1.36	1.41	0.82	1.20
Minimum, Maximum	0.6, 10.4	0.0, 3.6	0.0, 3.1	0.0, 10.4
BPDCN at Baseline[2], n (%)				
Bone Marrow Disease	3 (50.0)	5 (38.5)	7 (53.8)	15 (46.9)
Peripheral Blood Disease	2 (33.3)	2 (15.4)	3 (23.1)	7 (21.9)
Skin Disease	6 (100)	12 (92.3)	13 (100)	31 (96.9)
Lymph Node Disease	1 (16.7)	6 (46.2)	6 (46.2)	13 (40.6)
Visceral Disease	1 (16.7)	1 (7.7)	2 (15.4)	4 (12.5)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; mITT = modified Intent-to-Treat; StD = Standard Deviation.
[1] Time since BPDCN diagnosis is calculated as date of informed consent – date of diagnosis.
[2] Peripheral blood disease at baseline was defined as clinician detected evidence or presence of leukemic blasts where patient did not have a subsequent overall response assessment that indicated no evidence of disease at baseline. Bone marrow disease at baseline was defined as blasts measured by biopsy or aspirate of >5%. Skin disease at baseline was defined as positive skin biopsy result or non-zero mSWAT assessment. Lymph node disease at baseline was defined as presence of tumours in the lymph nodes where post baseline response assessments did not indicate no evidence of disease at baseline. Visceral mass disease at baseline was defined as presence of tumours or disease-related enlargement of the liver or spleen where post baseline response assessments did not indicate no evidence of disease at baseline.

Table 41. Primary Disease Characteristics: Relapsed/Refractory BPDCN, Overall and by Stage (mITT Population)

Parameter / Statistic	Stage 1 (N=3)	Stage 2 (N=10)	Stage 4 (N=2)	Overall (N=15)
Time Since BPDCN Diagnosis (months)[1]				
N	3	10	2	15
Mean (standard deviation)	16.70 (9.423)	25.91 (25.240)	3.99 (1.975)	21.14 (22.022)
Median	12.19	13.70	3.99	11.96
Minimum, Maximum	10.4, 27.5	6.2, 84.4	2.6, 5.4	2.6, 84.4
BPDCN at Baseline[2], n (%)				
Bone marrow disease	1 (33.3)	7 (70.0)	1 (50.0)	9 (60.0)
Peripheral blood disease	0	1 (10.0)	0	1 (6.7)
Skin disease	3 (100)	9 (90.0)	1 (50.0)	13 (86.7)
Lymph node disease	1 (33.3)	5 (50.0)	2 (100)	8 (53.3)
Visceral disease	1 (33.3)	3 (30.0)	0	4 (26.7)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; mITT = modified Intent-to-Treat. Time since BPDCN diagnosis is calculated as date of informed consent – date of diagnosis.
[2] Peripheral blood disease at baseline was defined as clinician detected evidence or presence of leukemic blasts where patient did not have a subsequent overall response assessment that indicated no evidence of disease at baseline. Bone marrow disease at baseline was defined as blasts measured by biopsy or aspirate of >5%. Skin disease at baseline was defined as positive skin biopsy result or non-zero mSWAT (modified severity-weighted assessment tool) assessment. Lymph node disease at baseline was defined as presence of tumours in the lymph nodes where post baseline response assessments did not indicate no evidence of disease at baseline. Visceral mass disease at baseline was defined as presence of tumours or disease-related enlargement of the liver or spleen where post baseline response assessments did not indicate no evidence of disease at baseline.

Numbers analysed

mITT

The mITT population was the primary population for the analysis of efficacy parameters. This population was defined as all patients who were eligible, based on the entrance criteria, and received at least 1 dose of SL-401 liquid solution. For BPDCN patients to be eligible for mITT, they must also have had confirmed diagnosis of disease, based on central pathology review. Patients with "inconclusive: likely BPDCN" disease, based on central pathology review, also were included. All 47 BPDCN patients, including 32 with first-line BPDCN, of whom 29 received SL-401 at 12 µg/kg/day, and 15 with R/R BPDCN, of whom all received SL-401 at 12 µg/kg/day, were included.

ADA Analysis

90% (28/31) and 93% (13/14) of the 1L and R/R BPDCN patients, respectively, were ADA-positive at baseline. Among them, results showed that; i) 21% (6/28) and 23% (3/13) of the 1L and R/R BPDCN patients, respectively, presented neutralising antibodies (NAb-positive) at baseline, ii) 96% and 85% of the 1L and R/R BPDCN patients, respectively, presented boosted ADA after being administered tagraxofusp, and iii) the maximum fold increased titer for treatment boosted-ADA for 1L BPDCN patients was of 100,000 and was reached at C2D15, C2D21 and C4D21; for R/R BPDCN patients was of 1.000.000 and was reached at C2D21.

Among the evaluable ADA-negative BPDCN patients at baseline (9% - 3/31 and 7% - 1/13, 1L and R/R, respectively), results showed; i) 100% of the 1L and R/R BPDCN patients presented boosted ADA after

tagraxofusp, and ii) the peak positive titer was reached at C2D15 for the all the BPDCN population (for more details see discussion on clinical safety).

AIA Analysis

Almost all of the patients were AIA-negative at baseline; only 1 patient (7%) from the R/R BPDCN population was AIA-positive. Results showed similar results for both 1L and R/R BPDCN population with incidence of treatment-induced AIA between 90 – 92% and a maximum fold increased titer of 51200 that was reached at C3D15. At the same incidence of total AIA-positive after treatment (94% vs 93%), Results of total AIA Nab-positive incidence was higher for 1L patients (96%) compared to R/R patients (77%) (for more details see discussion on clinical safety).

Outcomes and estimation

Efficacy Analyses in First-Line BPDCN Patients

A summary of the CR rate in Stage 3, including the KM analysis of duration of CR, is presented in Table 42, and the KM plot of duration of CR is displayed in Figure 11 for Stage 3 (as well as for first-line BPDCN patients in Stages 1 and 2 and in Stages 1, 2, and 3 combined).

Table 42. CR Rate and Kaplan-Meier Analysis of Duration of CR in First-Line BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

		Stage		
Parameter	Statistic	3 (N=13)	1 and 2 (N=16)	1, 2, and 3 (N=29)
CR Rate[1]	N (%)	7 (53.8)	14 (87.5)	21 (72.4)
	(95% CI)[2]	(25.1, 80.8)	(61.7, 98.4)	(52.8, 87.3)
Number with PD after CR	N (%)	1 (14.3)	6 (42.9)	7 (33.3)
Number Censored[3]	N (%)	6 (85.7)	8 (57.1)	14 (66.7)
Duration of CR (months)[4]	25th Percentile	NE	2.5	5.9
	(95% CI)	(7.3, NE)	(1.3, NE)	(1.3, NE)
	50th Percentile (Median)	NE	NE	NE
	(95% CI)	(7.3, NE)	(1.5, NE)	(5.9, NE)
	75th Percentile	NE	NE	NE
	(95% CI)	(7.3, NE)	(NE, NE)	(NE, NE)
	Range (Min, Max)[5]	(3.91, 12.22)	(1.31, 32.23)	(1.31, 32.23)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; CI = Confidence Interval; CR = Complete Response; CRc = CR with minimal residual skin abnormality; Max = Maximum; Min = Minimum; mITT = Modified Intent-to-Treat; NE = Nonestimable; PD = Progressive Disease.
1 Number and percentage of patients who achieved CR (CR+CRc) after treatment with SL-401.
2 Clopper-Pearson exact 95% CI.
3 Patients lost to follow-up or who did not relapse after CR (CR+CRc) as of the cutoff for analysis were censored at the date of last disease assessment while on study.
4 Duration of CR = Time from date of first CR (CR+CRc) (whichever is recorded first) to date of relapse after CR (CR+CRc) was met. Duration of response includes time to disease relapse post-transplant for patients who received a stem cell transplant after CR (CR+CRc) was observed.
5 Range may change over time as some patients are still on study.
Source: Table 14.2.13.1A.

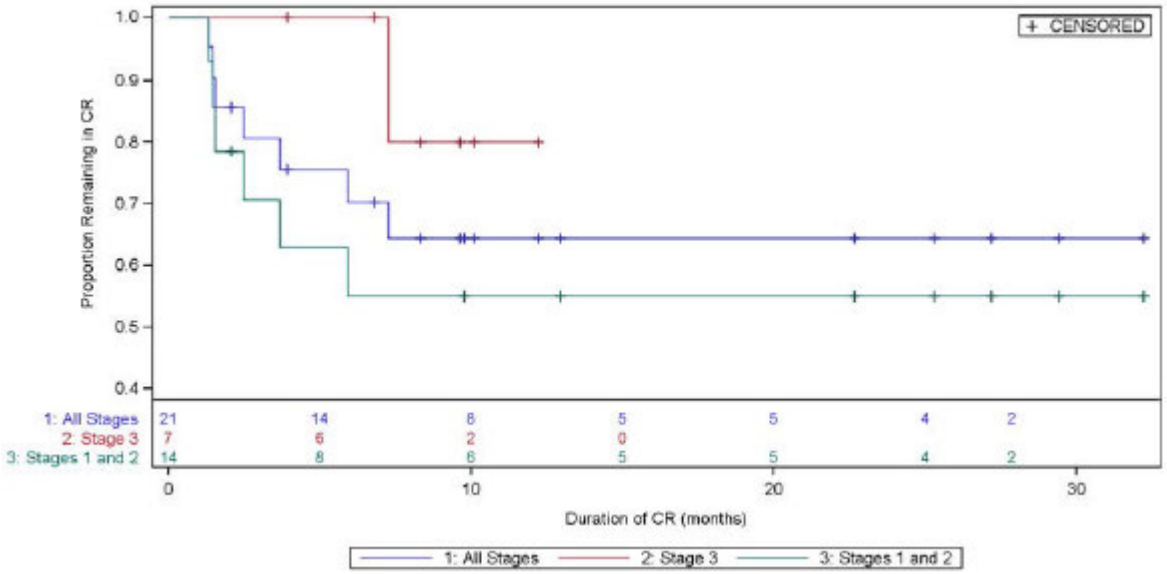


Figure 10. Kaplan-Meier Analysis of Duration of CR in First-Line BPDCN Patients Treated at 12 µg/kg/day, by Stage (mITT Population)

Table 43 - Response Rates in First line BPDCN Patients (12mcg/Kg) by Age (Study STML-40100114, Stages 1-4)

		<60years N=17	>60 to<65 years N=9	65 to<75 years N=28	>75years N=11
CR/CRc	N(%) 95%CI	10 (58.8) (32.9,81.6)	5 (55.6) (21.2, 86.3)	16 (57.1) (37.2,75.5)	6 (54.5) (23.4,83.3)
OR	N (%) 95% CI	13 (76.5) (50.1, 93.2)	5 (55.6) (21.2, 86.3)	22 (78.6) (59.0, 91.7)	9 (81.8) (48.2, 97.7)
Duration of OS (months)	Median (Range) 95% CI	38.4 4.7, 47.2 (38.4 , NE)	9.7 0.23, 12.32 0.2, 12.3	9.8 0.20, 49.74 6.9, 25.8	12.0 0.30, 27.66 0.3, 18.2

Abbreviations CI= confidence interval, CR=complete response, CRc-complete response with minimal residual skin abnormality, NE-not estimable, OS-overall survival
Source Table 2C, Table 3C, Table 4C

Table 44. Summary of Selected Efficacy Measures for First-Line BPDCN Patients Treated with Tagraxofusp at 12 µg/kg/day Who Experienced an Objective Response in stages 1 to 3 (Study 0114)

Patient Identification	Stage	Age (Years)	Best Response	Time to Best Response (Days)	Duration of OR (Days)	Duration of Treatment	SCT Type	Time to SCT (Days)[1]	Survival (Days)[2]
Patients Bridged to SCT:									
[redacted]	3	[redacted]	CR	57	307+	37	Allogenic	76	363+
	3		CRc	81	161+	110	Allogenic	135	223
	2		PR	17	519+	55	Other*	88	535+
	3		CR	107	338+	82	Allogenic	146	360+
	1		CR	22	981+	159	Autologous	198	1002+
	2		CRc	43	828+	74	Autologous	111	870+
	2		CR	22	297+	145	Autologous	190	361
	2		CR	20	690+	131	Allogenic	167	709+
	3		CR	63	241+	182	Allogenic	203	269+
	3		CRc	44	316+	95	Allogenic	118	336+
	3		CRc	14	372+	75	Allogenic	96	385+
	2		CR	49	798+	81	Allogenic	140	818+
	2		CR	49	63+	75	Allogenic	110	124
Patients not Bridged to SCT:									
[redacted]	2	[redacted]	CR	131	500+	524+	-	-	524+
	2		PR	21	27	138	-	-	418+
	2		CR	50	68	138	-	-	211
	2		CRc	39	201	222	-	-	549
	3		CRc	22	221	111	-	-	333+
	1		CR	45	47	118	-	-	294
	2		CR	32	896+	927+	-	-	927+
	2		CRc	39	112	131	-	-	632+
	2		CR	24	75	145	-	-	364
	3		PR	97	25	103	-	-	159
	3		PR	23	21	77	-	-	181
	1		CR	43	44	69	-	-	375
	3		PR	20	43	46	-	-	349+

Abbreviations: Allo=allogeneic; Auto=autologous; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = complete response with minimal residual skin abnormality; ID = identification; PR = partial response; OR = objective response; SCT = stem cell transplant.
Note: '+' denotes ongoing at the time of analysis.
*Haploidentical stem cells from child.
Patient died without evidence of disease progression and was censored at the latter of last date of exposure or last disease assessment.
[1]Time from treatment initiation.
[2]Time from the date of first infusion of tagraxofusp to the date of death from any cause

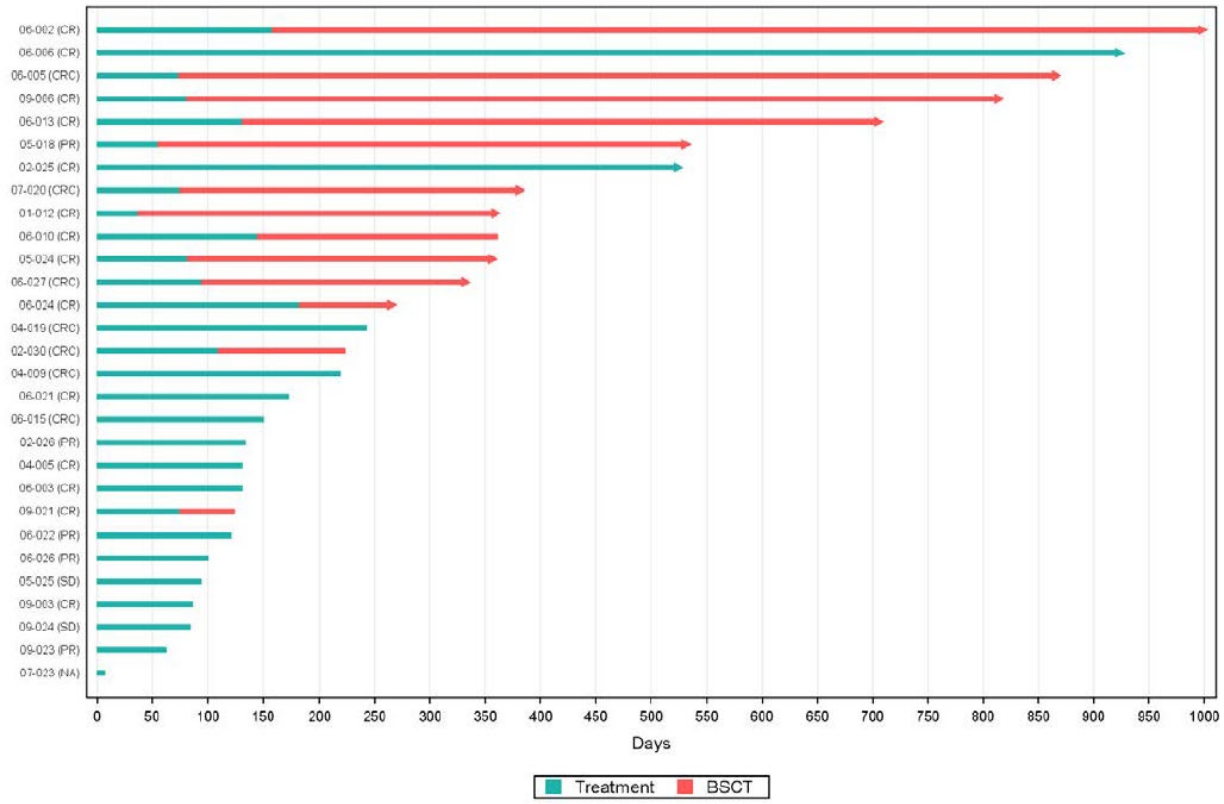


Figure 11. Swimmer Plot of Disease Outcomes for All First-Line BPDCN Patients stages 1 to 3 (mITT Population)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; BSCT = blood stem cell transplant; CR = Complete Response; CRc = Complete Response with Minimal Residual Skin Abnormality; mITT = Modified Intent-to-Treat; NA = not available; PR = Partial Response; SD = Stable Disease.
Note: Colour of bar represents treatment on tagraxofusp (blue) and time post BSCT (red) for patients who were bridged to SCT. For patients who were not bridged to SCT, blue bar includes time post-treatment in response. Arrow at the termination of the bar indicates patient was ongoing in response at the data cutoff and no arrow indicates time of progression.

Time to CR was assessed as an exploratory endpoint, with results showing a median time to CR of 43 days (first and third quartile range 24.0, 50.0 days).

Bone Marrow Complete Response Rate

BMCR was analysed only in patients with BM disease (i.e., >5% BM blast cells) at baseline (N=14).

Table 45. BMCR Rate and Kaplan-Meier Analysis of Duration of BMCR in First-Line BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

		Stage		
Parameter	Statistic	3 (N=13)	1 and 2 (N=16)	1, 2, and 3 (N=29)
BM Disease at Baseline	N	7	7	14
BMCR Rate[1]	N (%)	6 (85.7)	7 (100)	13 (92.9)
	(95% CI)[2]	(42.1, 99.6)	(59.0, 100)	(66.1, 99.8)
BMCR by Overall Response[1]				
BMCR with Overall CR Rate	N (%)	5 (71.4)	7 (100)	12 (85.7)
BMCR with Overall CRi Rate	N (%)	0	0	0
BMCR with Overall PR Rate	N (%)	1 (14.3)	0	1 (7.1)
Number with PD after BMCR	N (%)	2 (33.3)	4 (57.1)	6 (46.2)
Number Censored[3]	N (%)	4 (66.7)	3 (42.9)	7 (53.8)
Duration of BMCR (months)[4]	25th Percentile	7.3	1.4	3.5
	(95% CI)	(1.4, NE)	(1.4, 6.4)	(1.4, NE)
	50th Percentile (Median)	NE	6.4	NE
	(95% CI)	(1.4, NE)	(1.4, NE)	(1.4, NE)
	75th Percentile	NE	NE	NE
	(95% CI)	(7.3, NE)	(3.5, NE)	(7.3, NE)
	Range (Min, Max)	(1.41, 11.10)	(1.41, 29.44)	(1.41, 29.44)

Abbreviations: BM = Bone marrow; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; BMCR = Bone Marrow Complete Response; CI = Confidence Interval; CR = Complete Response; CRi = Complete Response with Incomplete Blood Count Recovery; mITT = Modified Intent-to-Treat NE = Nonestimable; PD = Progressive disease; PR = Partial Response.
Note: Patients with BM disease include patients with >5% BM blast cells at baseline.
1 Number and percentage of patients with an overall response of CR (CR, CRc), CRi, or PR who achieved BMCR after treatment with SL-401. Percent based on number with BM disease at baseline.
2 Clopper-Pearson exact 95% CI.
3 Patients lost to follow-up or who did not relapse after CR, CRi, or PR as of the cutoff for analysis were censored at the date of last on study disease assessment without progression. Patients who did not have BM disease at baseline were excluded from the analysis
4 Duration of BMCR = Time from date of BMCR (defined in footnote [1]) to date of relapse after BMCR is met. Duration of BMCR includes time to disease relapse post-transplant for patients who received a stem cell transplant after BMCR was observed. Relapse may occur in any disease compartment.

Time to BMCR was assessed as an exploratory endpoint, with results showing a median time to BMCR of 25 days (first and third quartile range 22.0, 39.0).

Objective Response Rate

A summary of the ORR in first-line BPDCN patients, including the KM analysis of duration of OR, is presented in Table 46.

Table 46. ORR and Kaplan-Meier Analysis of Duration of OR in First-Line BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

		Stage		
Parameter	Statistic	3 (N=13)	1 and 2 (N=16)	1, 2, and 3 (N=29)
ORR[1]	N (%)	10 (76.9)	16 (100.0)	26 (89.7)
	(95% CI)[2]	(46.2, 95.0)	(79.4, 100.0)	(72.6, 97.8)
Best Response				
CR	N (%)	3 (23.1)	11 (68.8)	14 (48.3)
CRc	N (%)	4 (30.8)	3 (18.8)	7 (24.1)
CRi	N (%)	0	0	0
PR	N (%)	3 (23.1)	2 (12.5)	5 (17.2)
SD	N (%)	2 (15.4)	0	2 (6.9)
PD	N (%)	0	0	0
Not Evaluable	N (%)	1 (7.7)	0	1 (3.4)
Number with PD after OR	N (%)	4 (40.0)	7 (43.8)	11 (42.3)
Number Censored[3]	N (%)	6 (60.0)	9 (56.3)	15 (57.7)

Parameter	Statistic	Stage 3 (N=13)	Stage 1 and 2 (N=16)	Stage 1, 2, and 3 (N=29)
Duration of Objective Response (months)[4]	25th Percentile	1.4	2.2	2.2
	(95% CI)	(0.7, NE)	(0.9, NE)	(0.8, 7.3)
	50th Percentile (Median)	NE	NE	NE
	(95% CI)	(0.7, NE)	(2.2, NE)	(2.5, NE)
	75th Percentile	NE	NE	NE
	(95% CI)	(7.3, NE)	(NE, NE)	(NE, NE)
	Range (Min, Max)	(0.69, 12.22)	(0.89, 32.23)	(0.69, 32.23)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; CI = Confidence Interval; CR = Complete Response; CRc = CR with Minimal Residual Skin Abnormality; CRi = CR with Incomplete Blood Count Recovery; Max = Maximum; Min = Minimum; mITT = Modified Intent-to-Treat; NE = Nonestimable; OR = Objective response; ORR = Objective Response Rate; PR = Partial Response; PD = Progressive Disease; SD = Stable disease.
1 Number and percentage of patients who achieved objective response defined as CR (CR+CRc), CRi, or PR after treatment with SL-401.
2 Clopper-Pearson exact 95% confidence interval.
3 Patients lost to follow-up or who did not relapse after CR (CR+CRc), CRi, or PR as of the cutoff for analysis are censored at the date of last disease assessment while on study.
4 Duration of OR = Time from date of first CR (CR+CRc), CRi, or PR (whichever is recorded first) to date of relapse after CR (CR+CRc), CRi, or PR was met. Duration of response included time to disease relapse post-transplant for patients who received a stem cell transplant after OR was observed.

Of the 26 first-line BPDCN patients with an OR, the duration of OR was >6 months (range 201 to 981+ days [32.2+ months]) for 15 patients and >12 months (i.e., 360 days) (range 372+ to 981+ days [32.2+ months]) for 8 patients as of 31 Jan 2018; the median duration of OR was not reached (range 0.7 to 32.2+ months).

Bridge to Stem Cell Transplantation

A total of 13 (45%; CI 26.4, 64.3%) of 29 first-line BPDCN patients in stage 1 to 3 treated with SL-401 at 12 µg/kg/day were successfully bridged to SCT. Of the 13 patients bridged to SCT, 3 underwent autologous SCT and 10 underwent allogeneic SCT (1 of whom received haploidentical stem cells donated by his child). The median time from the first SL-401 dose to SCT was 135 days (range 76 to 203 days). The interval between the last SL-401 dose and SCT ranged from 22 to 65 days (median 37 days).

A total of 77% (10/13) of patients who were bridged to SCT were alive with ongoing response as of 31 Jan 2018. Among the 10 patients who underwent SCT and who were alive with ongoing DOR, response durations ranged from 241+ to 981+ days, with the DOR >6 months for all 10 patients; >12 months for 6 patients; and >2 years for 3 patients. Of these 10 patients, 6 were aged <65 years and 4 were aged ≥65 years. Three of 13 patients who underwent SCT, all aged >65 years, had died as of 31 Jan 2018. Among the 13 patients who achieved an OR but who did not undergo SCT, 6 (46.2%) were alive at the time of the 31 Jan 2018 data cut-off, with survival ranging from 11 to 30 months, including 2 patients with long-standing and ongoing response durations (17 and 30 months, respectively), and 4 patients who had progressed with DOR ranging from <1 month to 7 months). Seven of these 13 patients had died between 5 and 18 months after the start of SL-401.

Overall Survival

Table 47. Kaplan-Meier Analysis of Overall Survival in First-Line BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

		Stage		
Parameter	Statistic	3 (N=13)	1 and 2 (N=16)	1, 2, and 3 (N=29)
Number of Deaths	N (%)	6 (46.2)	7 (43.8)	13 (44.8)
Number Censored	N (%)	7 (53.8)	9 (56.3)	16 (55.2)
Duration of OS (months)	25th Percentile	5.9	11.9	7.3
	(95% CI)	(0.2, NE)	(4.1, NE)	(5.1, 12.3)
	50th Percentile (Median)	NE	NE	18.0
	(95% CI)	(5.2, NE)	(11.9, NE)	(9.7, NE)
	75th Percentile	NE	NE	NE
	(95% CI)	(7.3, NE)	(NE, NE)	(18.0, NE)
	Range (min, max)	(0.23, 12.65)	(4.07, 32.92)	(0.23, 32.92)
Survival Probability:				
At 12 Months	%			59.3
	(95% CI)			38.0, 75.4
At 18 Months	%			54.3
	(95% CI)			33.0, 71.5
At 24 Months	%			46.6
	(95% CI)			24.2, 66.3

Note: CI = Confidence Interval; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; mITT = Modified Intent-to-Treat; NE = Non-estimable; OS = Overall Survival.
Note: Overall survival is defined as the time from the date of first infusion of SL-401 to the date of death from any cause. Patients still alive or lost to follow-up at the time of the analysis are censored on the last date known to be alive prior to the analysis cut-off date.
Note: Survival Probability from product limit method. Confidence limits constructed using log-log transformation.
Source: Table 14.2.18.1.

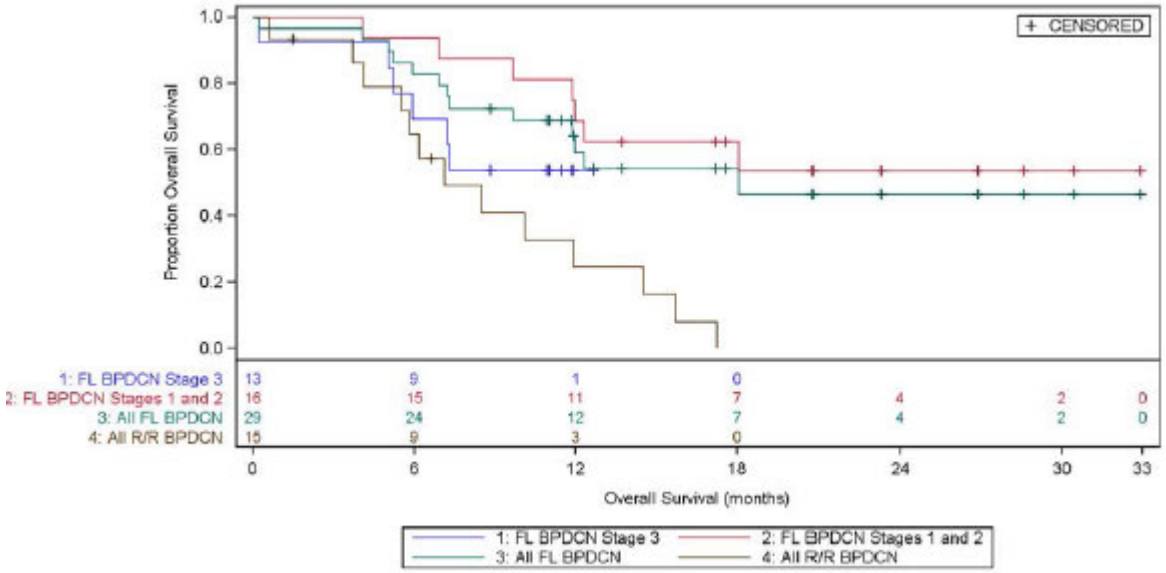


Figure 12. Kaplan-Meier Analysis of Overall Survival in BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

Progression-free Survival

Table 48. Kaplan-Meier Analysis of Progression Free Survival in First-Line BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

Table 14.2.17.1

Kaplan-Meier Analysis of Progression Free Survival (PFS) in BPDCN Patients Treated at 12 µg/kg/day (mITT Population)

		First-Line BPDCN Patients		All Stages BPDCN Patients	
	Statistic	Stage 3 (N=13)	Stage 1 & 2 (N=16)	First-Line (N=29)	Relapsed/Refractory (N=15)
PFS events	N (%)	8 (61.5)	9 (56.3)	17 (58.6)	14 (93.3)
Disease progression	N (%)	6 (46.2)	7 (43.8)	13 (44.8)	13 (86.7)
Deaths	N (%)	2 (15.4)	2 (12.5)	4 (13.8)	1 (6.7)
Number Censored	N (%)	5 (38.5)	7 (43.8)	12 (41.4)	1 (6.7)
Duration of PFS (months)	25th Percentile	3.1	4.4	4.1	0.7
	(95% CI)	(0.2, 7.3)	(2.8, 7.2)	(2.8, 4.9)	(0.5, 2.2)
	50th Percentile (Median)	7.3	9.5	7.3	2.6
	(95% CI)	(2.8, NE)	(4.3, NE)	(4.3, NE)	(0.6, 3.6)
	75th Percentile	NE	NE	NE	3.6
	(95% CI)	(4.0, NE)	(7.2, NE)	(11.9, NE)	(2.2, 15.7)
	Range (min, max)	(0.23, 12.65)	(2.83, 32.92)	(0.23, 32.92)	(0.53, 15.70)

Note: CI = Confidence Interval, PD = Progressive Disease, PFS = Progression-Free Survival, SCT = Stem cell transplant, BPDCN = Blastics Plasmacytoid Dendritic Cell Neoplasm, NE = Non-estimable.
Note: Progression-free survival is defined as the time from the date of first infusion of SL-401 to the date of PD or death from any cause, whichever occurred first. For patients who receive SCT, PFS includes time to PD or death post-transplant. Patients who do not progress and are still alive at the time of analysis are censored on the date of last on-study disease assessment without progression recorded prior to the analysis cut-off date.

Relapse-free Survival (Exploratory Endpoint)

As of 31 Jan 2018, median RFS was 11.2 months (range 1.3 to 32.2+ months) among the 21 first-line BPDCN patients treated with SL-401 at 12 µg/kg/day who achieved a best response of CR (N=14) or CRc (N=7). By 31 Jan 2018, 10 (48%) patients who had achieved a best response of CR or CRc had died or experienced PD.

Efficacy Analyses in Patients with Relapsed/Refractory BPDCN

A summary of efficacy measures for patients with R/R BPDCN treated with SL-401 liquid solution at 12 µg/kg/day who experienced an OR is presented in Table 48.

Table 49. Summary of Efficacy Measures for Relapsed/Refractory BPDCN Patients Treated with SL-401 at 12 µg/kg/day Experiencing an OR (mITT Population)

Patient (Stage)	Age (years)	Best Response	Time to Best Response (days)	Duration of OR (days)	Duration of Treatment (Days)	SCT Type	Time to SCT (days)[1]	Survival (days)[2]
Bridged to SCT								
[redacted]		CRc	46	424+	104	Allo	138	478
Patients Who Did Not Undergo SCT								
[redacted]		CRi	23	23+	8	-	-	45+
		PR	21	107	138	-	-	525
		PR	21	48	68	-	-	442
		CRi	48	46	97	-	-	169
		CR	82	111	117	-	-	308
		PR	29	22	34	-	-	177
		PR	21	89	94	-	-	259
		CRi	81	29	46	-	-	217
		PR	44	37	70	-	-	363

Abbreviations: Allo=Allogeneic; CR = Complete Response; CRc = CR with Minimal Residual Skin Abnormality; CRi = Complete Response with Incomplete Blood Count Recovery; mITT = Modified Intent-to-Treat; PR = Partial Response; OR = Objective Response; SCT=Stem Cell Transplant.
'+' denotes ongoing.
1 Time from treatment initiation
2 The time from the date of first infusion of SL-401 to the date of death from any cause.
Source: Listing 16.2.4.1, Listing 16.2.5.1C, Listing 16.2.6.20, Listing 16.2.6.21, and Listing 16.2.6.22.

Objective Response Rate

A summary of the ORR in all R/R BPDCN patients treated with SL-401 at 12 µg/kg/day, including the KM analysis of DOR, is presented in Table 50.

Table 50. ORR and Kaplan-Meier Analysis of Duration of OR in Relapsed/Refractory BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

Parameter	Statistic	All Stages Relapsed/Refractory BPDCN Patients (N=15)
ORR[1]	N (%)	10 (66.7)
	(95% CI)[2]	(38.4, 88.2)
Best Response		
CR	N (%)	1 (6.7)
CRc	N (%)	1 (6.7)
CRi	N (%)	3 (20.0)
PR	N (%)	5 (33.3)
SD	N (%)	1 (6.7)
PD	N (%)	4 (26.7)
Not Evaluable	N (%)	0
Number with PD after OR	N (%)	8 (80.0)
Number Censored[3]	N (%)	2 (20.0)
Duration of OR (months)[4]	25th Percentile	1.2
	(95% CI)	(0.7, 1.6)
	50th Percentile (Median)	1.6
	(95% CI)	(0.7, 3.6)
	75th Percentile	3.5
	(95% CI)	(1.5, NE)
	Range (Min, Max)	(0.72, 13.93)

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; CI = Confidence Interval; CR = Complete Response; CRc = CR with minimal residual skin abnormality; CRi = Complete Response with Incomplete Blood Count Recovery; Max = Maximum; Min = Minimum; mITT = Modified Intent-to-Treat; NE = Nonestimable; OR = Objective Response; ORR = Objective Response Rate; PR = Partial Response; PD = Progressive Disease; SD = Stable Disease.
1 Number and percentage of patients who achieved objective response defined as CR (CR+CRc), CRi, or PR after treatment with SL-401.
2 Clopper-Pearson exact 95% CI.
3 Patients lost to follow-up or who did not relapse after CR (CR+CRc), CRi, or PR as of the cutoff for analysis were censored at the date of last disease assessment while on study.
4 Duration of OR = Time from date of first CR (CR+CRc), CRi, or PR (whichever was recorded first) to date of relapse after CR (CR+CRc), CRi, or PR was met. Duration of response included time to disease relapse post-transplant for patients who received a stem cell transplant after OR was observed.

Complete Response Rate

The CR rate among R/R BPDCN patients was 13% (2/15) (95% CI: 1.7, 40.5).

Time to CR was assessed as an exploratory endpoint, with results showing a median time to CR of 64 days (first and third quartile range 46.0, 82.0).

An exploratory sensitivity analysis was performed on the rate of CR+CRc plus CRi. In this sensitivity analysis, the CR rate was 33% (5/15) among all R/R BPDCN patients.

Bone Marrow Complete Response

A summary of the BMCR rate in R/R BPDCN patients treated with SL-401 at 12 µg/kg/day with BM disease at baseline is presented in Table 51.

Table 51. BMCR Rate and Kaplan-Meier Analysis of Duration of BMCR in Relapsed/Refractory BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

Parameter	Statistic	All Stages Relapsed/Refractory BPDCN Patients (N=15)
BM Disease at Baseline	N	9
BMCR Rate[1]	N (%)	6 (66.7)
	(95% CI)[2]	(29.9, 92.5)
BMCR by Overall Response[1]		
BMCR with Overall CR Rate	N (%)	2 (22.2)
BMCR with Overall CRi Rate	N (%)	1 (11.1)
BMCR with Overall PR Rate	N (%)	3 (33.3)
Number with PD after BMCR	N (%)	5 (83.3)
Number Censored[3]	N (%)	1 (16.7)
Duration of BMCR (months)[4]	25th Percentile	1.0
	(95% CI)	(0.7, 3.6)
	50th Percentile (Median)	2.4
	(95% CI)	(0.7, NE)
	75th Percentile	4.3
	(95% CI)	(1.0, NE)
	Range (Min, Max)	(0.72, 13.93)

Abbreviations: BM = bone marrow; BMCR = Bone Marrow Complete Response; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; CI = Confidence Interval; CR = Complete Response; CRc = CR with minimal residual skin abnormality; CRi = Complete Response with Incomplete Blood Count Recovery; Max = Maximum; Min = Minimum; mITT = modified Intent-to-Treat; PD = Progressive Disease; NE = Nonestimable; PR = Partial response.
Note: Patients with BM disease include patients with >5% BM blast cells at baseline.
1 Number and percentage of patients with an overall response of CR (CR, CRc), CRi, or PR who achieved BMCR after treatment with SL-401. Percent based on number with BM disease at baseline.
2 Clopper-Pearson exact 95% CI.
3 Patients lost to follow-up or who did not relapse after CR, CRi, or PR as of the cutoff for analysis are censored at the date of last on study disease assessment without progression. Patients who did not have BM disease at baseline are excluded from the analysis.
4 Duration of BMCR = Time from date of BMCR (defined in footnote 1) to date of relapse after BMCR is met. Duration of BMCR includes time to disease relapse post-transplant for patients who received a stem cell transplant after BMCR was observed. Relapse may occur in any disease compartment.
Source: Table 14.2.14.1B.

Bridge to Stem Cell Transplantation

Of note, 1 (7%) patient with R/R BPDCN was bridged to SCT; this patient experienced a best response of CRc to SL-401 before allogeneic SCT.

Overall Survival

The KM analysis of duration of OS among R/R BPDCN patients treated with SL-401 12 µg/kg/day, is presented in Table 52.

Table 52. Kaplan-Meier Analysis of Duration of OS in Relapsed/Refractory BPDCN Patients Treated with SL-401 at 12 µg/kg/day (mITT Population)

	Statistic	Relapsed/Refractory BPDCN Patients (N=15)
Number of Deaths	N (%)	13 (86.7)
Number Censored	N (%)	2 (13.3)
Duration of OS (months)	25th Percentile	5.6
	(95% CI)	(0.6, 7.1)
	50th Percentile (Median)	7.1
	(95% CI)	(4.1, 11.9)
	75th Percentile	11.9
	(95% CI)	(7.1, 17.2)
	Range (min, max)	(0.59, 17.25)
Survival at 12 Months	N	13
Alive at 12 Months	n (%)	3 (23.1)
Deaths Prior to 12 Months	n (%)	10 (76.9)
Survival Probability	%	24.6
	(95% CI)	6.1, 49.5

Abbreviations: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; CI = Confidence Interval; mITT = modified Intent-to-Treat; Max = Maximum; Min = Minimum; OS = Overall Survival.
Note: Overall survival is defined as the time from the date of first infusion of SL-401 to the date of death from any cause. Patients still alive or lost to follow-up at the time of the analysis are censored on the last date known to be alive prior to the analysis cut-off date.
Note: Survival Probability from product limit method. Confidence limits constructed using log-log transformation.
Source: Table 14.2.18.1.

Progression-free Survival

Among all 15 R/R BPDCN patients, median PFS was 2.6 months (range 0.5 to 15.7 months) as of 31 Jan 2018; by this time, 14 (93%) of 15 patients had died or experienced PD.

Relapse-free Survival

median RFS was 8.9 months (range 3.7 to 14.2 months) among the 2 R/R BPDCN patients treated with SL-401 at 12 µg/kg/day who achieved a best response of CR. By that time, both patients who had achieved CR had died (1 patient) or experienced PD (1 patient).

Ancillary analyses

Due to the small number of patients, subgroup analyses were neither planned nor performed for efficacy endpoints.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application for the liquid formulation. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 53. Summary of Efficacy for trial STML-401-0114 liquid formulation

Title: SL-401 in patients with acute myeloid leukemia or blastic plasmacytoid dendritic cell neoplasm	
Study identifier	STML-401-0114

Design	nonrandomized, open-label, single-arm, multicenter study of SL-401 divided into 4 stages		
	Duration of main phase:		SL-401 was administered as a daily infusion for up to 5 consecutive days of a 21-day cycle, initially for up to 6 cycles, with the potential to receive additional cycles, with the approval of the Medical Monitor.
Hypothesis	Exploratory, stage 3 confirmatory		
Treatments groups	Patients with First-Line BPDCN in Stage 3		SL-401 at 12 µg/kg/day daily intravenous (IV) infusion over 15 minutes for up to 5 consecutive days of a 21-day cycle, with no maximum duration of therapy N=13
	Patients with First-Line BPDCN in Stages 1 and 2		SL-401 at 12 µg/kg/day daily intravenous (IV) infusion over 15 minutes for up to 5 consecutive days of a 21-day cycle, with no maximum duration of therapy (N=16)
	All Patients with First-Line BPDCN		SL-401 at 12 µg/kg/day daily intravenous (IV) infusion over 15 minutes for up to 5 consecutive days of a 21-day cycle, with no maximum duration of therapy (N=29)
	All Patients with R/R BPDCN		SL-401 at 12 µg/kg/day daily intravenous (IV) infusion over 15 minutes for up to 5 consecutive days of a 21-day cycle, with no maximum duration of therapy (N=15).
Endpoints and definitions	Primary endpoint	CR rate	Percentage of patients who achieved CR (CR+CRc) after treatment with SL-401 in first-line BPDCN patients in Stage 3.
	Secondary endpoint	Duration of CR in first-line BPDCN patients in Stage 3	-Time from when the criteria were first met for CR+CRc (whichever was recorded first) until the date that the criteria for relapse after CR+CRc were met.
	Secondary endpoint	BMCR and duration of BMCR	-BMCR rate was measured by pooling data from patients who had either CR or PR who achieved reduction to ≤5% BM blast cells, as a proportion of all patients with marrow disease at baseline. -time from when criteria were first met for BMCR until the date that the criteria for relapse were met, including PR, SD, PD, or relapse in BM compartment or SD, PD, or relapse in any other disease compartment.
	Secondary endpoint	CR (CR+CRc) rate and duration of CR	for Stages 1 and 2 and for pooled data from Stages 1, 2, and 3
	Secondary endpoint	ORR and duration of objective response	(CR+CRc+CRi+PR) for Stages 1 and 2 and for pooled data from Stages 1, 2, and 3.
	Secondary endpoint	Proportion of patients who received SCT	for pooled data from all stages
	Secondary endpoint	PFS	-time from the date of first infusion of SL-401 to the date of PD or death from any cause, -for all stages pooled

	Secondary endpoint	OS	-the time from the date of first infusion of SL-401 to the date of death from any cause. -for all stages pooled
Database lock	31 Jan 2018		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified Intent to treat: all patients who were eligible, based on the entrance criteria, and received at least 1 dose of SL-401. For BPDCN patients, they must also have had confirmed diagnosis of disease, based on central pathology review.				
Descriptive statistics and estimate variability	Treatment group	Patients with First-Line BPDCN in Stage 3	Patients with First-Line BPDCN in Stages 1 and 2	All Patients with First-Line BPDCN	All Patients with R/R BPDCN
	Number of subject	13	16	29	15
	CR rate n/N (%) 95% CI	7/13 (53.8) 25.1, 80.8	14/16 (87.5) 61.7, 98.4	21/29 (72.4) 52.8, 87.3	2/15 (13.3) 1.7, 40.5
	Duration of CR Median (95% CI) (months) Range (Min, Max)	NE (7.3, NE) 3.91, 12.22	NE (1.5, NE) 1.31, 32.23	NE (5.9,NE) 1.31, 32.23	NE (3.6,NE) 3.65, 13.93
	Time to CR (days) Median (Q1, Q3)	57.0 (22.0, 81.0)	41.0 (24.0, 49.0)	43.0 (24.0, 50.0)	64.0 (46.0, 82.0)

	BMCR Rate n/N (%) 95% CI	6/7 (85.7) 42.1, 99.6	7/7 (100) 59.0, 100	13/14 (92.9) 66.1, 99.8	6/9 (66.7) 29.9, 92.5
	Duration of BMCR (months) Median Range (Min, Max)	NE 1.4, 11.1	6.4 1.4, 29.4	NE 1.4, 29.4	2.4 0.7, 13.9
	Time to BMCR (days) Median (Q1, Q3)	26.0 (22.0, 39.0)	25.0 (22.0, 43.0)	25.0 (22.0,39.0)	45.0 (29.0, 81.0)
	ORR n/N (%) 95% CI	10/13 (76.9) 46.2, 95.0	16/16 (100) 79.4, 100	26/29 (89.7) 72.6, 97.8	10/15 (66.7) 38.4, 88.2
	Duration of OR (month) (95% CI) Range (Min, Max)	NE (0.7, NE) 0.7, 12.2	NE (2.2, NE) 0.9, 32.2	NE (2.5, NE) 0.7, 32.2	1.6 (0.7, 3.6) 0.7, 13.9
	Time to OR (days) Range (Min, Max)	23.0 14, 97	23.0 17, 49	23.0 14, 97	36.5 21, 82
	Bridge to SCT n/N (%)	6/13 (46.2)	7/16 (43.8)	13/29 (44.8)	1/15 (6.7)
	PFS (months) Median (95% CI)	7.3 (2.8, NE)	9.5 (4.3, NE)	7.3 (4.3, NE)	2.6 (0.6, 3.6)
	OS (months) Median (95% CI)	NE (5.2, NE)	NE (11.9, NE)	18.0 (9.7, NE)	7.1 (4.1, 11.9)
	RFS Median (95% CI)	NE (4.7, NE)	8.5 (1.5, NE)	11.2 (3.7, NE)	8.9 (3.6, 14.2)

Additional data from stage 4

Efficacy data from Stage 4 (N=44) of Study 0114 have been provided during the procedure. In this Stage 4, 37 first-line BPDCN patients and 5 R/R BPDCN patients received the lyophilised formulation of tagraxofusp at 12 µg/kg/day, which represents the largest cohort of the study 0114. Among the 37 first-line BPDCN patients, CR rate was 44.4% (16/36) (95% CI: 27.9, 61.9) and ORR was 63.9% (23/36) (95% CI: 46.2, 79.2). Median durations of CR and ORR were both 3.9 months (95% CI: 0.72, 23.33). Median PFS was 3.1 months (95% CI: 1.8, 4.8) and median OS was 9.8 months (95% CI: 6.6, 18.2). The number of patients bridged to HSCT was 22%.

Efficacy results are summarised as follows.

Table 54. Efficacy Summary in First-Line BPDCN Patients Treated With 12 mcg/kg of tagraxofusp

	Stage 1-2 (Liquid DP) (N=16)	Stage 3 (Pivotal; Liquid DP) (N=13)	Stage 4 (Lyo DP) (N=36) [1]
Response Rate			
Objective Response			
n (%)	16 (100.0)	10 (76.9)	23 (63.9)
(95% CI)	(79.4, 100.0)	(46.2, 95.0)	(46.2, 79.2)
CR/CRc	14 (87.5)	7 (53.8)	16 (44.4)
Cri	0	0	0
PR	2 (12.5)	3 (23.1)	7 (19.4)
CR/CRc, % [2]			
Probability of CR/CRc ≥ 6 months	50.0	85.8	40.0
Probability of CR/CRc ≥ 12months	42.9	71.4	30.0
Probability of CR/CRc ≥ 18 months	42.9	57.1	30.0
Probability of CR/CRc ≥ 24 months	42.9	57.1	30.0
Bridged to SCT			
n (%)	7 (43.8)	6 (46.2)	8 (22.2)
Median Age (years) [3]	65	61	58
Overall Survival, % [2]			
OS-12	68.8	53.8	41.8
OS-18	62.5	53.8	36.6
OS-24	56.3	46.2	24.4

Source: Table 2E, Efficacy Table 3A, Efficacy Table 6A.1, Efficacy Table 7A.
Note: duration of response includes time post-SCT in patients that received SCT in remission.
[1] One patient withdrew consent prior to the first response assessment and is excluded from the efficacy dataset.
[2] CR/CRc and OS probabilities calculated from product limit method.
[3] Age at study entry.

Table 55. Efficacy Summary in R/R Patients Treated With 12 mcg/kg of tagraxofusp

	Liquid DP (N=15)	Lyophilized DP (N=4) [1]	Total (N=19)
Response Rate			
Objective Response			
n (%)	10 (66.7)	1 (25.0)	11 (57.9)
(95% CI)	(38.4, 88.2)	(0.6, 80.6)	(33.5, 79.7)
CR/CRc	2 (13.3%)	1 (25.0)	3 (15.8)
Cri	3 (20.0%)	0	3 (15.8)
PR	5 (33.3%)	0	5 (26.3)
Overall Survival			
Median OS (months)	8.5	4.7	8.2
Range (min, max), months	0.59, 27.07	1.08, 16.36	0.59, 27.07

Source: Efficacy Table 3B, Efficacy Table 7B.
[1] One patient withdrew consent prior to the first response assessment and is excluded from the efficacy analysis.

Analysis performed across trials (pooled analyses and meta-analysis)

In Study 0114, a total of 29 patients with first-line BPDCN were treated with the proposed to be marketed dose of 12 µg/kg/day of tagraxofusp across 3 stages (Stages 1-2: N=16 and Stage 3: N=13) (Table 56). For this analysis, data from 28 of the 29 patients who had at least one post-baseline response assessment were included; one patient in Stage 3 who did not have any post-baseline assessments was excluded. Patients enrolled in Stage 3 generally presented with higher disease burden in the skin and bone marrow, the 2 predominant sites of disease in patients with BPDCN.

Table 58 presents baseline disease burden in skin and BM by stage. Given the apparent numerical difference between Stages 1-2 compared to Stage 3 in the rates of CR/CRc potentially related to the stability of the results, a Bayesian approach was used to estimate the probability distribution of the CR/CRc rate. The assumption of a beta prior distribution results in a 95% credible interval on the CR/CRc rate parameter of (66.1%, 98.2%). Subsequently, a 95% percent credible interval on the posterior distribution of the CR/CRc rate parameter using the prior distribution from Stages 1-2 updated by the likelihood of the Stage 3 data was calculated as (53.7%, 86.2%), which is a more reliable estimate of the true CR/CRc rate since it appropriately adjusts for all data.

Table 56. Comparison of Efficacy Results in First-Line BPDCN Patients Treated with Tagraxofusp at 12 µg/kg/day, by Stage of Enrollment

Parameter	Stages 1 and 2 (N=16) n (%)	Stage 3 (N=12)[1] n (%)
Overall Response Rate (95% CI)	16 (100) (79.4, 100)	10 (83.3) (51.6, 97.9)
CR/CRc Rate (95% CI)	14 (87.5) (61.7, 98.4)	7 (58.3) (27.7, 84.8)
Bridged to SCT, n (%)	7 (43.8)	6 (50.0)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = complete response with minimal residual skin abnormality; SCT = stem cell transplant.

[1] Patient 07-023 did not have any response assessment post-baseline, so while the patient is included in the mITT population, for the purpose of assessing responses to therapy the patient is excluded from this table.

Source: Study 0114 CSR Ad Hoc Table 14.2.13.1C, Ad Hoc Table 14.2.15.1C and Table 12.

The below table presents the updated efficacy data including Stage 4 of the Study 0114.

Table 57. Efficacy Summary in First-Line Patients Treated With 12 mcg/kg of Tagraxofusp (Pool stage 1 - 4)

	First-Line BPDCN (N=65)
Response Rate	
Objective Response	
n (%)	49 (75.4)
(95% CI)	(63.1, 85.2)
CR/CRc	37 (56.9)
Cri	0
PR	12 (18.5)
CR/CRc, % (95% CI) [1]	
n (%)[2]	37 (56.9)
(95% CI)	(44.0, 69.2)
Probability of CR/CRc ≥ 6 months	52.8 (35.5, 67.4)
Probability of CR/CRc ≥ 12months	43.5 (26.9, 58.9)
Probability of CR/CRc ≥ 18 months	39.8 (23.5, 55.7)
Probability of CR/CRc ≥ 24 months	39.8 (23.5, 55.7)
Bridged to SCT	
n (%)	21 (32.3)
Median Age (years)	63
Overall Survival, % (95% CI) [1]	
OS-12	52.2 (38.5, 64.2)
OS-18	48.2 (34.6, 60.5)
OS-24	40.9 (27.5, 53.9)

Source: Table 2E, Efficacy Table 3A, Efficacy Table 6A.1, Efficacy Table 7A.
Note: duration of response includes time post-SCT in patients that received SCT in remission.
[1] CR/CRc and OS probabilities calculated from product limit method.
[2] One patient withdrew consent prior to the first response assessment and is excluded from the efficacy analysis.
[3] Age at study entry.

Table 58. Comparison of Baseline Disease Burden in Skin and Bone Marrow in First-Line BPDCN Patients Treated with Tagraxofusp at 12 µg/kg/day, by Stage of Enrollment

Parameter	Stages 1 and 2	Stage 3[1]
Baseline skin disease[2], N	15	12
Tertile 1, n (%) (Total mSWAT score >25%)	3 (20)	6 (50)
Tertile 2, n (%) (Total mSWAT score 5-25%)	6 (40)	3 (25)
Tertile 3, n (%) (Total mSWAT score <5%)	6 (40)	3 (25)
Baseline bone marrow disease, N	7	7
Tertile 1, n (%) (Blasts >60%)	1 (29)	4 (57)
Tertile 2, n (%) (Blasts 25-60%)	4 (57)	1 (14)
Tertile 3, n (%) (Blasts 5-<25%)	2 (29)	2 (29)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; mSWAT = modified severity weighted assessment tool.
1 Excludes Patient 07-023 who did not have any response assessment post-baseline.
2 Includes patients with reported baseline mSWAT; 1 patient did not have a reported mSWAT but had a skin biopsy positive for BPDCN.
Source: Study 0114 CSR Listing 16.2.6.26, Listing 16.2.6.27 and Listing 16.2.6.33A.

Clinical studies in special populations

No clinical studies in special population were conducted. Three paediatric patients have been treated under investigator-sponsored single-patient INDs, including a 10-year-old female with R/R BPDCN, a 12-year-old female with R/R BPDCN, and a 15-year-old female with previously-treated BPDCN. All 3 patients received tagraxofusp at 12 µg/kg administered intravenously over 15 minutes once daily on days 1 to 5 every 2 to 3 weeks. Skin disease and BM disease were present in 2 patients each. Two of the 3 paediatric patients experienced response to treatment; however, the responses were of short duration.

Table 59. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	0	0	0
Non Controlled trials	17	13	0

Supportive study

Study 50047

Study 50047 was an Investigator-sponsored study of tagraxofusp in patients with advanced haematologic malignancies. An expansion arm was added to evaluate tagraxofusp in patients with

BPDCN. The results have been published (Frankel, 2013; Frankel, 2014). Patients were either relapsed/refractory (R/R) or first-line but deemed not to be candidates for standard chemotherapy. A single cycle of tagraxofusp was administered intravenously at 12 µg/kg over 15 minutes once daily on days 1 to 5 of a 21-day cycle. BPDCN response criteria were based on published recommendations (Cheson, 2003; Cheson, 2007; Pagano, 2016) and are outlined in Table 60.

Table 60. Study 50047: BPDCN response criteria

Response	Criteria
CR	Normalisation of peripheral blood and BM, absence of disease on PET/CT imaging, normal liver and spleen size without nodules, and absence of skin involvement documented by examination and biopsy of previously affected areas.
PR	A decrease in BM blasts, >50% decrease in the SPD of up to 6 of the largest dominant nodal masses, no increase in the size of other lymph nodes, >50% decrease in SPD of spleen or liver nodules, no increase in the size of the liver or spleen, and >50% decrease in skin lesions.
SD	Failure to achieve a PR in patients without BM involvement and without evidence of disease progression in skin/lymph nodes/liver/spleen.
PD	Death during treatment or disease progression with persistence of >5% BM blasts or any new lymph nodes or new skin lesions or increase from nadir by >50% of SPD of any single previously involved lymph node or total assessed lymph node masses or >50% increase from nadir in the SPD of liver or spleen nodules or >50% increase in liver or spleen size.

Abbreviations: BM = bone marrow; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CT = computed tomography; PD = progressive disease; PET = positron emission tomography; PR = partial response; SD = stable disease; SPD = sum of the product of the diameters.
Source: (Frankel, 2014).

Six patients had disease limited to the skin, and 5 had BM disease with or without skin, nodal, or splenic involvement. The treatment regimen for all patients included a single cycle of therapy; 7 patients received all 5 doses, 2 patients received a single dose, and 1 patient each had 2 or 3 doses. Three patients received a second course after disease relapse. Nine BPDCN patients were evaluable for response, i.e., had at least one response assessment, including 4 first-line patients and 5 R/R patients.

The objective response rate (ORR) was 78% (7/9), with 5 complete responses (CRs) and 2 partial responses (PRs):

- Among the 4 first-line patients, the ORR was 100% (4/4), including 2 CRs.
- Among the 5 R/R patients, the ORR was 60% (3/5), comprised of 3 CRs.

The median response duration across the 11 patients was 5 months, with a range of 1 to 20+ months, including 4 patients with ongoing remissions at the time of the analysis:

- One first-line patient who achieved a CR was alive and in remission at 33 months (remission ongoing at the time of the update).
- Three R/R patients who achieved a CR survived >12 months in remission, including 1 patient who survived 30 months in remission.

Notably, normalization of blood counts was observed, often within 4 weeks, without an interim period of myelosuppression.

2.5.3. Discussion on clinical efficacy

Assessment of clinical efficacy of tagraxofusp in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) is mainly based on the results from the Phase I/II study STML-401-0114 (Study 0114).

In all study stages, the recommended dose of tagraxofusp is 12 µg/kg administered as an intravenous infusion over 15 minutes, once daily, on days 1 to 5 of a 21-day cycle. Two different pharmaceutical forms (solution vs powder) were administered to the full study population.

Tagraxofusp was administered initially for up to 6 cycles with the potential to receive additional cycles. By amendment 8 (08 Feb 2016), the patients may continue to receive tagraxofusp if they benefitted from treatment according to the investigators with no maximum duration of therapy.

The first cycle of tagraxofusp was administered in the in-patient setting and patients were monitored until at least 24 hours after the last infusion. For subsequent treatment cycles, tagraxofusp could be administered in the in-patient setting or in a suitable out-patient ambulatory care setting that was equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, at the discretion of the Investigator and according to institutional guidelines and capabilities; patients were monitored for at least 4 hours following the administration of each infusion of tagraxofusp.

Patients were pre-medicated with a H1-histamine antagonist (e.g. diphenhydramine hydrochloride), a H2-histamine antagonist (e.g. ranitidine), a corticosteroid (e.g. 50 mg intravenous methylprednisolone or equivalent) and paracetamol approximately 60 minutes prior to the start of infusion.

In addition, preliminary efficacy data had been obtained from an Investigator-sponsored first in human study (Study 50047) which the aim was to select the intended dose and schedule of administration for a larger Phase 2 clinical trial. Nevertheless, it was conducted without entering data into a formal database and limited resolution of data queries was possible.

Design and conduct of clinical studies

At the time of scientific advice (EMEA/H/SA/3101/1/2015/SME/III), a placebo with the option of cross-over at progression or investigator's choice of therapy in the control arm were proposed as comparators, but the sponsor did not include it in the study design. A nonrandomised, open-label and single-arm design was chosen for the Study 0114. According to the CHMP (EMEA/H/SA/3101/1/2015/SME/III), a single uncontrolled pivotal study might be considered acceptable to support a MAA, if it provides; i) an acceptable design, ii) robust and convincing results that are externally valid, and iii) sufficient safety information to allow estimation of the benefit/risk. However, many uncertainties would remain about the robustness of evidence that can be produced in single-arm trials, and further, in a small sample size.

Scientific advice from the CHMP (EMEA/H/SA/3101/1/FU/1/2017/SME/II) was sought on the design and analysis plan of the Stage 3 pivotal efficacy cohort. The CHMP position was that in the context of such a rare disease, analysis of the totality of data (pooled Stages 1-4) would be preferable for the benefit-risk assessment. Thus, in addition to presenting the efficacy analysis of Stage 3, an analysis where first-line patients were pooled from stages 1-3 is also included.

The inclusion/exclusion criteria were generally agreed by the CHMP (EMEA/H/SA/3101/1/2015/SME/III) and were the same across Stages 2-4, with the exception that only first-line BPDCN patients were eligible for Stage 3. This facilitates pooling for efficacy analysis. Importantly, the diagnosis criteria for BPDCN was according to the WHO classification and in addition to local pathologic assessment, pathology material was also submitted for central pathology review to

confirm the diagnosis. CNS leukaemia was listed as an exclusion criterion in this study. This can be understood from a classic oncology study design where this patient group is normally excluded from the study population. However, a recent study reports CNS involvement in ~60% of the BPDCN cases despite lack of neurological symptoms. Information in the SmPC alert about the fact that patients with CNS leukaemia were not included in the study, that the passage of tagraxofusp through the blood brain barrier is unknown and that other treatment alternatives should be considered if CNS disease is present.

The primary efficacy endpoint of the pivotal cohort (Stage 3) was to determine the CR rate (ie, CR + complete response with minimal residual skin abnormality [CRc]) in patients with first-line BPDCN. Considering that there are no established global response criteria for BPDCN, the applicant had proposed an initial definition of CR including CR + CRc + complete response with incomplete blood count recovery (CRi). To validate and analyse the clinical benefit of these response criteria, patients from Stage 1 and Stage 2 were used to measured DOR of CR, CRc and CRi and assess the likelihood that these durations are derived from the same probability distribution. From this analysis, CR and CRi did not demonstrate comparability in terms of duration of the response whereas comparability between CR and CRc was observed. Then, the definition of CR was amended into the actual definition (CR= CR + CRc).

Due to the complexity of the BPDCN disease that involves different organs, different response criteria used to assess the specific organ involvement in similar disease were combined. Measurements of skin disease burden were calculated using the modified Severity Weighted Assessment Tool (mSWAT) which is a method for skin scoring that has been used in clinical trials for other malignancies. This approach was considered as acceptable by the CHMP (EMEA/H/SA/3101/1/2015/SME/III).

In the context of a single-arm trial in which the magnitude of response rate is unknown to be predictive of long-term clinical benefit, an effect of clinical relevance may be considered when the outcome of CR rate is supported by duration of response (DoR) and SCT rate. Other secondary endpoints were also included: achievement of BMCR, PFS and OS. These endpoints were endorsed by SAWP (EMEA/H/SA/3101/1/FU/1/2017/SME/II).

Except for the primary endpoint in Stage 3, the applicant has not specifically defined endpoints in the different subgroups including the R/R population. Moreover, no secondary endpoints have been explicitly described for these subgroups, except for the Stage 3 cohort. Generally, use of endpoints in the study could have been better defined.

Of note, the study 0114 was not sized to detect a particular magnitude of an effect for R/R BPDCN population. No multiplicity adjustments were pre-specified and none of the two primary endpoints was pre-defined for formal statistical testing. The overall statistical analysis was accepted by the CHMP as part of a scientific advice. However, these results need to be interpreted with caution.

Efficacy data and additional analyses

Dose response studies

The first in human clinical study of tagraxofusp was an investigator-sponsored study (Study 50047) in which 2 dosing regimens were evaluated; regimen A (doses every other day for up to 6 doses, 2 weeks of inpatient setting) vs regimen B (a daily × 5 schedule every 21 days, 1 week of inpatient setting). The selected schedule was the regimen B to improve drug delivery and patient compliance, as patients were hospitalised for 1 week rather than 2 weeks. Dose-limiting toxicities at the highest dose of 22.1 µg/kg/day were observed. Based on the totality of the data, the 12.5 µg/kg/day was identified as

the RP2D based on a favourable risk/benefit profile, with a low incidence of adverse reactions and multiple major tumour responses after a single cycle of therapy.

The purpose of Study 0114 was to confirm the previous Phase 1/2 experience with tagraxofusp in Study 50047). Upon completion of Stage 1 and analysis of the dose escalation results, the MTD was determined to be 16 µg/kg/day in patients with AML; this dose was not tested in patients with BPDCN, as responses were observed at the 12 µg/kg/day dose in this patient population. For BPDCN patients, the RP2D, 12 µg/kg administered intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle.

In the study 0114, 3 first-line BPDCN patients received tagraxofusp at 7 µg/kg/day, 29 first-line BPDCN patients (including 13 patients from stage 3) received tagraxofusp at 12 µg/kg/day, and 15 R/R BPDCN patients received tagraxofusp at 12 µg/kg/day. At DCO, only 2 (4.3%) BPDCN patients were still ongoing at study 0114.

Baseline characteristics were generally similar between the first-line and R/R BPDCN populations, and are in line with published descriptions concerning age, sex and disease characteristics excluding the race distribution for this disease population. Worldwide population is not fully represented as only USA sites were selected. However, taking into account that almost all the enrolled population were white (93.1%) and that baseline characteristics were closely matched to the published literature concerning BPDCN, it can be expected that the study population will very likely reflect the disease population in EU. Based on this, extrapolation of the existing data to the EU population covered by the claimed therapeutic indication is considered acceptable.

In relation to the baseline characteristics of the BPDCN population, the main disease location was skin (96.9% first-line and 86.7% R/R), bone marrow (46.9% first-line and 60.0% R/R) and lymph nodes (40.6% first-line and 53.3% R/R). Patients presented peripheral blood and visceral disease, as well; first-line patients presented a higher incidence of peripheral blood disease (21.9% first-line and 6.7% R/R) whereas R/R presented a higher incidence of visceral disease (12.5% first-line and 26.7% R/R).

Among the 31 first-line BPDCN patients who had skin disease at baseline: the skin was the only disease manifestation at time of diagnosis for 16 patients (50.0%) whereas skin and other organs/systems were involved for 15 patients (46.9%). Ten patients (31.3%) had no extramedullary involvement.

Twelve (80%) of the 15 R/R BPCN patients were refractory to their most recent line of systemic chemotherapy/immunotherapy. The number of prior lines of therapy was 1 for 8 (53%) patients, 2 or 3 for 4 (27%) patients each, and ≥4 for 2 (13%) patients. In general, the included population is considered highly heterogeneous.

Efficacy

First-line BPDCN

- Stage 3 (N=13)

The CR rate (CR +CRc) in the confirmatory Stage 3 cohort was 53.8% (7/13) bounded within a 95% CI of 25.1 to 80.8, which exceeded the pre-specified rate. Therefore, the study is considered positive as the primary endpoint was met. Median duration of the CR was not reached through a median duration follow-up of 20.0 months.

Positive results were also seen in further secondary endpoints; among the 7 first-line BPDCN patients with BM disease at baseline, BMCR rate was 85.7% (6/7) (95% CI: 42.1% - 99.6%) and the median duration of the BMCR was not reached.

However, these results should be interpreted with caution due to the low number of patients analysed.

- All patients with first-line BPDCN (N=29)

Among all 29 first-line BPDCN patients treated with tagraxofusp at 12 µg/kg/day, CR rate was 72.4% (21/29) (95% CI: 52.8, 87.3), ORR was 89.7% (26/29), with CR, CRc, CRi, and PR rates of 48.3% (14/29), 24.1% (7/29), 0%, and 17.2% (5/29), respectively. Median durations of CR and objective response (OR) were not reached through 3 October 2018, with a median duration of follow-up of 24.9 months (95% CI: 20.0, 30.6) in the updated time-to event analyses. Overall, 44.8% (13/29) patients were bridged to SCT with 10 patients of 13 (77%) alive and still in response as compared to those who did not undergo SCT where 2 of 16 patients (12.5%%; two in ongoing response after 24 and 43 cycles of treatment) were alive at the time of last data cut off. However, in the context of a single arm trial, it cannot be excluded that investigator's choice to proceed to HSCT was partly influenced by the knowledge of the type of treatment. Median PFS was 7.3 months (95% CI: 4.3- NE) and median OS was 18.0 months (95% CI: 9.7- NE). Among the 14 first-line BPDCN patients with BM disease at baseline, BMCR rate was 92.9% (13/14) (95% CI: 66.1% - 99.8%) and the median duration of the BMCR was not reached (see also below further discussion on the data).

It should be emphasised that retrospective studies suggested that induction therapy with regimens commonly used in non-Hodgkin lymphoma, AML and ALL yield high response rates (CR of 40-90%). However, these responses are short-lived with reported median OS ranging from 8 to 12 months except for patients who could benefit from allo-HSCT.

It cannot be excluded that some of the older patients that received tagraxofusp in study 0114 (median age was 67.5 years) might not have been healthy enough for chemotherapy as older patients with comorbidities generally do not tolerate this regimen very well. Thus, whether tagraxofusp treatment is superior to existing chemotherapy alternatives cannot be concluded from these response outcomes but it might be a more acceptable alternative for these patients.

The literature is rather limited concerning bridging to SCT, with few BPDCN patients in each report, and the majority of the cases reported in the literature concern younger patients with median age <60 years. In study 0114 elderly patients (54% were ⩾65 years old [range: 22 to 72 years]) have successfully been bridged to SCT, and whether this pertains to willingness in this study to bridge elderly patients, a higher number of elderly patients achieving CR, or a more healthy study population than what is met in clinical practise is not known.

The majority of patients developed high level of NAbs that had an impact on the free tagraxofusp exposure but no effect is likely to be expected on efficacy. The hypothesis that pharmacological effect persists despite binding is acceptable and the efficacy beyond the first cycle may seem to be supported by clinical data provided.

However, in the context of a single arm clinical trial with rather small population where contextualisation with available historical data is not feasible, the clinical relevance of the effect observed in first-line BPDCN patients remains uncertain. Positive results on OS were obtained, but the effect on OS presented in CSR seemed to be driven by the SCT itself more than the effect of tagraxofusp; median OS results presented for patients that did not undergo a transplantation were similar to outcomes obtained with regular chemotherapy.

R/R BPDCN (N=15)

Among all 13 R/R BPDCN patients treated with tagraxofusp at 12 µg/kg/day, CR rate was 13.3% (2/15) (95% CI: 1.7% - 40.5%) and ORR was 66.7% (10/15 – 95% CI: 38.4% - 88.2%). Median duration of CR was not reached through 17.3 months of median duration follow-up. Duration of median objective response (OR) was 1.6 months (95% IC: 0.7 - 13.9 months). Only one patient was bridged

to SCT. Median PFS was 2.6 months (95% CI: 0.6- 3.6) and median OS was 7.1 months (95% CI: 4.1-11.9). Among the 9 R/R BPDCN patients with BM disease at baseline, BMCR rate was 66.7% (6/9) (95% CI: 29.9% - 92.5%) and the median duration of the BMCR was 2.4 months.

Study 0114 was not designed to provide any conclusion on this population; no hypothesis, objectives or endpoints were planned for R/R BPDCN patients. Based on the exploratory results obtained for R/R BPDCN patients, the clinical benefit of the treatment with tagraxofusp in these patients is uncertain. Drawing any positive conclusion on the use of tagraxofusp in this population is thus hampered.

Efficacy supportive studies

In Study 50047, 11 patients with BPDCN have received tagraxofusp. Only 9 patients were evaluable; 4 first-line and 5 R/R BPDCN patients. In first-line BPDCN patients, CR rate was 50% (2/4) and ORR was 100% (4/4). Among R/R BPDCN patients CR rate and ORR were 60% (3/5).

Additional data from stage 4

New efficacy data from Stage 4 (N=44) of Study 0114 have been provided during the procedure. In this Stage 4, 37 first-line BPDCN patients and 5 R/R BPDCN patients received the lyophilised formulation of tagraxofusp at 12 µg/kg/day, which represents the largest cohort of the study 0114. Among the 37 first-line BPDCN patients, CR rate was 44.4% (16/36) (95% CI: 27.9, 61.9) and ORR was 63.9% (23/36) (95% CI: 46.2, 79.2). Median durations of CR and ORR were both 3.9 months (95% CI: 0.72, 23.33). Median PFS was 3.1 months (95% CI: 1.8, 4.8) and median OS was 9.8 months (95% CI: 6.6, 18.2). Only 4 R/R patients have been treated with lyophilized tagraxofusp in stage 4, which adds very limited new information about tagraxofusp response in this population. These data could only be consider supportive as both pharmaceutical forms are not comparable from a PK point of view. Further, supportive efficacy data from stage 4 did not bring reassurance as a lower efficacy profile in the target population was shown.

In summary, results showed heterogeneous response rate and overall survival in the different cohorts.

Additional expert consultation

The SAG oncology was consulted in relation to the following questions on the efficacy and safety of tagraxofusp:

1. **Is the response rate and other outcomes seen in study STML 401 0114 indicative that treatment with tagraxofusp would provide clinically relevant efficacy in first-line or R/R BPDCN?**

This question was debated at length, especially whether activity and benefits have been established, whether the level of efficacy can be considered relevant or not given the therapeutic context, and in which population the effect has been established.

Currently, patients with BPDC are treated when possible with intensive induction chemotherapy and allogeneic SCT, which is associated with long-term disease control and prolonged survival. Using this strategy, median survival has been improved from 8 months to 49 months. From pooled retrospective data on >140 patients, allogeneic stem cell transplantation is applicable in 42-44% of patients.

The same regimens are used for BPDCN as often used for adult patients with an ALL (or AML), and it is generally assumed that responses may be similar, or with a slight advantage for ALL-like regimens, but long-term outcomes are worse if patients do not undergo allogeneic transplant.

All SAG members agreed that antitumour activity of tagraxofusp has been shown in several patients, on the basis of 56.9% (95% C.I.: 44.0%, 69.2%) of patients meeting the criteria for CR/CRc. A

complete response was defined as the disappearance of disease in each site of initial disease. CRc was defined as complete response in all disease compartments with residual skin abnormality not indicative of active disease.

All members also agreed that some patients experienced durable responses and underwent allogeneic SCT, which is known to be associated with long-term benefits when associated with induction chemotherapy. If the ability to undergo allogeneic SCT was confirmed in patients with progressive disease for whom allogeneic SCT was not an option at the time of inclusion in the tagraxofusp trial, clinical relevant efficacy could be considered established.

However, the experts questioned whether the studied population clearly met the criteria of patients with progressive disease for whom allogeneic SCT was not an option. In general, the population was heterogenous with a proportion of relatively young and good performance status (0 or 1) patients so that it was not clear why intensive chemotherapy with allogeneic SCT would not have been an option. In fact, approximately 30% (10/29) of previously untreated patients went on to allo-SCT after tagraxofusp. It was also noted that a few patients proceeded to allogeneic SCT within only 4 to 12 weeks, which would be unexpected if this had not been an option when starting tagraxofusp.

The experts were also uncertain about how the level of efficacy would compare to established and available induction chemotherapies to be possibly followed by allogeneic SCT, in a population of patients eligible for allogeneic SCT. In particular, the SAG members could not exclude a potential detrimental effect in long-term outcomes compared to well-established and widely available induction chemotherapy regimens, due to the heterogeneous response rate and overall survival in the different cohorts, the short median follow-up, the small sample size, the variable prior treatments, the unknown phenotypes (i.e., if CD123 expression was present in 100% of cases) at study entry, the lack of reliable long-term data, the limited activity in relapsed patients, the sometimes very short duration of response and PFS, and generally an insufficient description of the disease and treatment characteristics of patients at entry (e.g., with respect to eligibility for allogeneic SCT), and at the time of SCT. Given that induction chemotherapy plus allogeneic SCT is a treatment option that is associated with long-term survival in approximately 50% of the patients, the risk of a detriment was considered a critical issue.

In conclusion, the SAG agreed that if Elzonris could be demonstrated to enable treatment with allogeneic SCT in patients for whom this treatment was not an option, due for instance to insufficient response to a chemotherapy-based induction regimen, then clinically relevant efficacy would be demonstrated. However, the experts were uncertain whether the current data and analyses presented have demonstrated this to be the case. The SAG also agreed that there were too many uncertainties to assess the efficacy of Elzonris in a transplant-eligible population, given the lack of long-term data in the submission.

Thus, the experts could not confirm that clinically relevant efficacy has been established. The SAG suggested that perhaps further analyses and updates of the data might alleviate some of the existing uncertainties. For example, a thorough clinical review of all patients treated, with detailed clinico-pathologic and therapeutic information for each individual patient, could help establishing which patients were clearly not eligible for allogeneic SCT, based on stringent criteria (e.g., lack of response to previous treatments), and then assess the role of Elzonris in enabling patients to become eligible. This would also be helpful in assessing the role of allogeneic SCT and other subsequent treatments on the overall clinical outcome. Also, with all the known caveats, exploratory landmark analyses of survival should be conducted to compare patients with or without CR, and patients who did or did not undergo allogeneic SCT. The survival of different cohorts, the survival by prior treatment, and the survival of patients with or without allogeneic SCT should also be explored based on updated survival data. Lastly, available post-marketing efficacy and safety data from where the product has been

approved (e.g., U.S.A.) should be presented, also to understand in which patients the product is used in clinical practice.

One expert stressed the fact that although it is unclear to what extent the data support this, assuming that the effect after transplant is similar as for intensive chemotherapy, this could likely be a useful alternative option in first-line treatment in patients not eligible for intensive chemotherapy and for whom the different toxicity profile could be of interest. However, due to the many uncertainties this treatment should not be indicated in younger patients, and in any case, confirmatory long-term data should be requested in a bigger cohort of patients.

2. **Is the safety profile of tagraxofusp in the target population acceptable?**

The toxicity profile of tagraxofusp is in principle acceptable given that haematologists are used to managing high incidences of haematological and non-haematological toxicity. However, the toxicity profile is significant, in particular, the capillary leak syndrome which was sometimes fatal.

Potential adverse events due to neutralizing antibodies remain a theoretical possibility although the SAG agreed that these were not a big concern.

3. **In what ways might tagraxofusp provide an advantage compared to currently used therapies?**

Theoretical advantages in patients unfit for intensive chemotherapy and allogeneic SCT have been claimed, but the data and analyses presented were unable to firmly substantiate such advantages. An additional therapeutic option would in principle be very welcome but should not put patients at risk of detriment in long term outcomes given widely available and well-established chemotherapy regimens. Therefore, the additional analyses mentioned under answers to questions 1 and 4 are strongly recommended.

4. **What further investigations are possible to characterise the efficacy and safety of tagraxofusp?**

Further investigations should be guided by the target indication.

For a transplant-eligible population, the objective should be to minimise potential loss of efficacy and if possible to improve safety. A randomised design against intensive chemotherapy or "investigator choice", even if not powered to detect small differences in survival, and with stringent criteria for eligibility for SCT could help addressing some of the uncertainties.

For a transplant ineligible population, see above as to additional data and analyses that could help addressing some of the uncertainties. Additional data should be collected in this population in a real-world registry, including baseline patient and disease characteristics, and the whole history of the disease, including different interventions and outcomes. Data should also be collected to explore mechanisms of resistance (e.g., loss of target expression and auto-antibodies).

2.5.4. Conclusions on the clinical efficacy

Efficacy results obtained for first line BPDCN population, including patients from all stages, showed an acceptable rate of complete responses (72.4%, median duration not reached) with patients that achieved bone-marrow complete response. In addition, there was important percentage of patients bridged to SCT, which represents the best chance to obtain long-term remission and long-term survival. However, contextualisation of the results was not possible.

Positive results on OS were obtained, as well, but the effect on OS presented in CSR seemed to be driven by the SCT itself more than the effect of tagraxofusp; median OS results presented for patients that did not undergo a transplantation were similar to outcomes obtained with regular chemotherapy.

Moreover, the single-arm trial design and the small sample size do not allow to conclude on the efficacy profile of tagraxofusp and supportive efficacy data from stage 4 did not bring reassurance as a lower efficacy profile in the target population was shown.

Regarding R/R BPDCN patients, the study 0114 was not designed to provide any conclusion on this population; no hypothesis, objectives or endpoints were planned for R/R BPDCN patients.

2.6. Clinical safety

This safety assessment is based on an integrated safety analysis from one ongoing non-randomised, open-label, multicentre study (STML-401-0114, hereafter Study 0114) of tagraxofusp monotherapy in 96 patients with AML (N=49) and BPDCN (N=47), and available data from 3 ongoing clinical studies with tagraxofusp in patients with haematological malignancies (STML-401-0214; N=16, STML-401-0314; N=29; STML-401-0414; N=7).

Patient exposure

BPDCN Patients in Study 0114

Table 61 presents summary of Patient Enrollment in Study 0114, by Disease, Tagraxofusp Dose and Stage.

Table 61. Summary of Patient Enrollment in Study 0114

Disease	Stage 1 N	Stage 2 N	Stage 3 N	Stage 4 N	Overall N
First-line BPDCN					
7 µg/kg/day	3	0	0	0	3
12 µg/kg/day	3	13	13	0	29
Total	***6***	***13***	***13***	***0***	***32***
R/R BPDCN					
12 µg/kg/day	3	10	0	2	15
Total	***3***	***10***	***0***	***2***	***15***
AML					
7 µg/kg/day	3	0	0	0	3
9 µg/kg/day	3	0	0	0	3
12 µg/kg/day	2	34	0	0	36
16 µg/kg/day	6	1[1]	0	0	7
Total	***14***	***35***	***0***	***0***	***49***
Overall	**23**	**58**	**13**	**2**	**96**

Abbreviations: AML = Acute Myeloid Leukaemia; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; R/R = Relapsed/Refractory.
1 One AML patient (06-018) was assigned to a dose of 12 µg/kg/day but received 16 µg/kg/day.
Source: Study 0114, Table 14.1.1A, Table 14.1.1B, Listing 16.2.5.1A, and Listing 16.2.5.1B.

Data through 31 Jan 2018, include 47 BPDCN patients who are the primary focus of the safety in this population.

Among the 32 first-line BPDCN patients, median duration of tagraxofusp exposure was 96 days (range 2, 927+ days); the median number of cycles started was 5.0, with 81% of patients starting at least 4 cycles of treatment.

Among the 15 R/R BPDCN patients, median duration of exposure was 48 days (range 6, 138 days); the median number of cycles started was 3.0, with 47% of patients starting at least 4 cycles of treatment.

All Applicant-Sponsored Studies

An overall summary of patient disposition in all applicant-sponsored studies is presented in Table 62, overall and by study.

Of the 148 patients, 141 received tagraxofusp as monotherapy only and 7 received tagraxofusp as monotherapy only for 1 cycle before receiving combination therapy with POM/DEX. Of the 141 patients treated with tagraxofusp monotherapy only:

- 12 received tagraxofusp at 7 µg/kg/day.
- 9 received tagraxofusp at 9 µg/kg/day.
- 113 received tagraxofusp at 12 µg/kg/day, the dose intended to be marketed.
- 7 received tagraxofusp at 16 µg/kg/day.

Table 62. Patient Enrollment and Disposition: All Patients in Applicant-Sponsored Studies, Overall and by Indication/Study (Safety Population)

	Stemline-Sponsored Study					
Parameter	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Study 0414 (N=7) n (%)	Total (N=148) n (%)
Safety Population[1]	47 (100.0)	49 (100.0)	16 (100.0)	29 (100.0)	7 (100.0)	148 (100.0)
Ongoing on Treatment at Data Cutoff[2]	2 (4.3)	0	0	8 (27.6)	0	10 (6.8)
Discontinued Treatment at Any Time[2]	45 (95.7)	49 (100.0)	16 (100.0)	21 (72.4)	7 (100.0)	138 (93.2)
Primary Reason for Treatment Discontinuation[3]						
Disease Recurrence/ Progression	23 (48.9)	25 (51.0)	9 (56.3)	10 (34.5)	2 (28.6)	69 (46.6)
Other[3]	15 (31.9)	5 (10.2)	1 (6.3)	2 (6.9)	0	23 (15.5)
Investigator's Decision	4 (8.5)	7 (14.3)	2 (12.5)	3 (10.3)	1 (14.3)	17 (11.5)
Adverse Event	2 (4.3)	8 (16.3)	2 (12.5)	4 (13.8)	1 (14.3)	17 (11.5)
Withdrawal of Consent	1 (2.1)	4 (8.2)	1 (6.3)	2 (6.9)	3 (42.9)	11 (7.4)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm.
1 All patients who received at least 1 dose of tagraxofusp.
2 Percentage based on total number of patients in Safety Population.
3 Study 0114 Listing 16.2.1.1 includes 'other' as a reason for discontinuation with additional information specified; 14/23 patients with 'other' listed as the reason for discontinuation were proceeding to receive a stem cell transplant.
Source: SCS Table 1.1.1.

A summary of exposure to tagraxofusp for the Summary of Clinical Safety (SCS) pool is presented in Table 63, overall and by study.

Table 63. Tagraxofusp Exposure: All Patients in the Summary of Clinical Safety Pool, by Indication/Study (Safety Population)

	Stemline-Sponsored Study			
Parameter	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)
Duration of Exposure (Days)[1]				
N	47	49	16	29
Mean (StD)	112.0 (145.50)	36.1 (68.32)	71.4 (67.82)	104.7 (108.27)
Median	82.0	6.0	51.0	72.0
Min, Max	2, 927	2, 410	2, 236	3, 406
Number of Cycles Started				
N	47	49	16	29
Mean (StD)	5.6 (6.60)	2.3 (2.94)	3.1 (2.13)	4.8 (3.5)
Median	4.0	1.0	2.5	4.0
Min, Max	1, 43	1, 18	1, 8	1, 14
Relative Dose Intensity[2]				
N	47	49	16	29
Mean (StD)	95.2 (10.10)	87.2 (20.06)	97.6 (5.84)	99.3 (3.87)
Median	99.8	100.0	100.0	100.0
Min, Max	40, 104	40, 103	80, 100	79, 100
Total Dose (µg)				
N	47	49	16	29
Mean (StD)	27242.2 (34101.64)	8614.9 (9217.27)	149.9 (124.86)	160.2 (123.73)
Median	21969.60	5270.00	112.5	144.0
Min, Max	1840, 23307	1507, 43550	21, 480	36, 504

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; Max = maximum; Min = minimum; StD = standard deviation.
1 Duration of exposure in days = (date of last dose - date of first dose) + 1.
2 Relative dose intensity = sum(cumulative dose administered during cycle)/sum(cumulative dose planned during cycle)
Source: SCS Table 1.2.1.1.

Baseline characteristics

Patients with BPDCN in Study 0114

When the data are examined by baseline status (i.e., first-line vs R/R):

• Among the 32 first-line BPDCN patients, most were male (26 patients; 81%) and white (30 patients; 94%). The median age of patients was 68 years, with a wide range of 22 to 84 years.

• Among the 15 R/R BPDCN patients, most were male (13 patients; 87%) and white (13 patients; 87%). The median age of patients was 72 years, with a range of 44 to 80 years.

All Applicant-Sponsored Studies

A summary of demographics and baseline characteristics among all patients in Stemline sponsored studies is presented in Table 64, overall and by study.

Table 64. Demographics: All Patients in Applicant-Sponsored Studies, Overall and by Indication/Study (Safety Population)

Parameter	Stemline-Sponsored Study					
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Study 0414 (N=7) n (%)	Total (N=148) n (%)
Gender, n (%)						
Male	39 (83.0)	29 (59.2)	12 (75.0)	15 (51.7)	4 (57.1)	99 (66.9)
Female	8 (17.0)	20 (40.8)	4 (25.0)	14 (48.3)	3 (42.9)	49 (33.1)
Race, n (%)						
White	43 (91.5)	43 (87.8)	14 (87.5)	20 (69.0)	7 (100.0)	127 (85.8)
Asian	2 (4.3)	1 (2.0)	0	6 (20.7)	0	9 (6.1)
Other	1 (2.1)	2 (4.1)	1 (6.3)	2 (6.9)	0	6 (4.1)
Black	0	3 (6.1)	1 (6.3)	1 (3.4)	0	5 (3.4)
Native American	1 (2.1)	0	0	0	0	1 (0.7)
Ethnicity, n (%)						
Hispanic or Latino	4 (8.5)	6 (12.2)	1 (6.3)	4 (13.8)	0	15 (10.1)
Not Hispanic or Latino	43 (91.5)	41 (83.7)	15 (93.8)	25 (86.2)	7 (100.0)	131 (88.5)
Missing	0	2 (4.1)	0	0	0	2 (1.4)
Age (years)						
N	47	49	16	29	7	148
Mean (StD)	64.9 (14.73)	60.4 (14.73)	63.8 (10.67)	68.3 (8.16)	65.3 (4.35)	64.0 (13.12)
Median	69.0	62.0	63.5	69.0	66.0	67.0
Min, Max	22, 84	21, 87	45, 82	42, 81	57, 69	21, 87
Age Category (years), n (%)						
<65	17 (36.2)	27 (55.1)	10 (62.5)	9 (31.0)	2 (28.6)	65 (43.9)
≥65	30 (63.8)	22 (44.9)	6 (37.5)	20 (69.0)	5 (71.4)	83 (56.1)
≥75[1]	13 (27.7)	9 (18.4)	2 (12.5)	6 (20.7)	0	30 (20.3)
Height (cm)						
N	44	46	16	19	6	131
Mean (StD)	172.0 (9.16)	169.7 (10.46)	173.9 (12.34)	166.1 (11.78)	164.6 (14.39)	170.2 (10.82)
Median	172.5	168.5	173.8	164.7	165.2	170.0
Min, Max	154, 190	152, 190	152, 207	146, 182	142, 182	142, 207
Missing	3	3	0	10	1	17
Weight (kg)						
N	47	49	16	19	7	138
Mean (StD)	86.8 (15.37)	80.7 (18.35)	81.8 (13.07)	70.9 (14.86)	85.7 (18.46)	81.8 (16.92)
Median	85.6	77.7	82.8	69.0	79.8	81.6
Min, Max	61.5, 128.2	56.9, 162.4	56.7, 107.5	46.7, 92.8	69.4, 122.6	46.7, 162.4
ECOG PS, n (%)						
0	22 (46.8)	11 (22.4)	8 (50.0)	3 (10.3)	3 (42.9)	47 (31.8)
1	25 (53.2)	34 (69.4)	7 (43.8)	14 (48.3)	4 (57.1)	84 (56.8)
2	0	3 (6.1)	1 (6.3)	2 (6.9)	0	6 (4.1)
Missing	0	1 (2.0)	0	10 (34.5)	0	11 (7.4)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; ECOG PS = Eastern Cooperative Oncology Group performance status; Native American = American Indian or Alaska Native; Black = Black or African American; Max = maximum; Min = minimum; StD = standard deviation.
1 The age categories ≥65 and ≥75 are not mutually exclusive (for example, an 80-year-old patient was counted in both categories).
Source: SCS Table 1.1.2.

Adverse events

Treatment-Emergent Adverse Events

BPDCN Patients in Study 0114

Summaries of TEAEs and of common (i.e., incidence ≥10%) TEAEs among all BPDCN patients are presented in Table 65 and Table 66, by MedDRA PT, sorted by total incidence among all BPDCN patients (N=47).

Table 65. Treatment-Emergent Adverse Events Summary: First-line and R/R BPDCN Patients in Study 0114, Overall and by Line of Therapy (Safety Population)

	Disease		
Patients with at least 1:	First-Line BPDCN Patients (N=32) n (%)	R/R BPDCN Patients (N=15) n (%)	Total BPDCN Patients (N=47) n (%)
TEAE	32 (100.0)	15 (100.0)	47 (100.0)
TEAE Related to Tagraxofusp	28 (87.5)	13 (86.7)	41 (87.2)
≥Grade 3 TEAE	25 (78.1)	13 (86.7)	38 (80.9)
≥Grade 3 TEAE Related to Tagraxofusp	20 (62.5)	10 (66.7)	30 (63.8)
SAE	13 (40.6)	10 (66.7)	23 (48.9)
SAE Related to Tagraxofusp	5 (15.6)	5 (33.3)	10 (21.3)
TEAE Leading to Discontinuation of Tagraxofusp	1 (3.1)	0	1 (2.1)
Tagraxofusp Related TEAE Leading to Discontinuation	1 (3.1)	0	1 (2.1)
Tagraxofusp Related TEAE Leading to Dose Reduction/Interruption	21 (65.6)	9 (60.0)	30 (63.8)
TEAE Occurring within 24 Hours of Dose	5 (15.6)	2 (13.3)	7 (14.9)
TEAE Leading to Dose Reduction	1 (3.1)	0	1 (2.1)
TEAE Leading to Dose Interruption	22 (68.8)	10 (66.7)	32 (68.1)
TEAE Leading to Death	2 (6.3)	1 (6.7)	3 (6.4)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; R/R = relapsed/refractory; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Study 0114, Table 14.3.1.1B.

Table 66. Most Common (≥10%) Treatment-Emergent Adverse Events: First-line and R/R BPDCN Patients in Study 0114, Overall and by Line of Therapy, by MedDRA Preferred Term (Safety Population)

	Disease		
MedDRA Preferred Term	First-Line BPDCN Patients (N=32)	R/R BPDCN Patients (N=15)	Total BPDCN Patients (N=47)
At Least 1 TEAE	32 (100)	15 (100)	47 (100)
Alanine aminotransferase increased	22 (68.8)	8 (53.3)	30 (63.8)
Aspartate aminotransferase increased	21 (65.6)	7 (46.7)	28 (59.6)
Hypoalbuminaemia	14 (43.8)	12 (80.0)	26 (55.3)
Oedema peripheral	13 (40.6)	11 (73.3)	24 (51.1)
Thrombocytopenia	16 (50.0)	7 (46.7)	23 (48.9)
Nausea	16 (50.0)	6 (40.0)	22 (46.8)
Fatigue	13 (40.6)	8 (53.3)	21 (44.7)
Pyrexia	11 (34.4)	10 (66.7)	21 (44.7)
Weight increased	13 (40.6)	5 (33.3)	18 (38.3)
Hyperglycaemia	11 (34.4)	6 (40.0)	17 (36.2)
Chills	9 (28.1)	7 (46.7)	16 (34.0)
Hypotension	7 (21.9)	6 (40.0)	13 (27.7)
Back pain	7 (21.9)	5 (33.3)	12 (25.5)
Decreased appetite	7 (21.9)	5 (33.3)	12 (25.5)
Headache	11 (34.4)	1 (6.7)	12 (25.5)
Anaemia	8 (25.0)	3 (20.0)	11 (23.4)
Constipation	10 (31.3)	1 (6.7)	11 (23.4)
Hypocalcaemia	7 (21.9)	4 (26.7)	11 (23.4)
Hypertension	6 (18.8)	4 (26.7)	10 (21.3)
Hypokalaemia	6 (18.8)	4 (26.7)	10 (21.3)
Anxiety	6 (18.8)	3 (20.0)	9 (19.1)
Capillary leak syndrome	5 (15.6)	4 (26.7)	9 (19.1)
Hyponatraemia	5 (15.6)	4 (26.7)	9 (19.1)
Diarrhoea	7 (21.9)	1 (6.7)	8 (17.0)
Dizziness	6 (18.8)	2 (13.3)	8 (17.0)
Hypomagnesaemia	5 (15.6)	3 (20.0)	8 (17.0)
Neutropenia	3 (9.4)	5 (33.3)	8 (17.0)
Vomiting	6 (18.8)	2 (13.3)	8 (17.0)

MedDRA Preferred Term	Disease		
	First-Line BPDCN Patients (N=32)	R/R BPDCN Patients (N=15)	Total BPDCN Patients (N=47)
Hyperuricaemia	4 (12.5)	3 (20.0)	7 (14.9)
Insomnia	5 (15.6)	2 (13.3)	7 (14.9)
Oropharyngeal pain	6 (18.8)	1 (6.7)	7 (14.9)
Tachycardia	6 (18.8)	1 (6.7)	7 (14.9)
Blood creatinine increased	3 (9.4)	3 (20.0)	6 (12.8)
Dyspnoea	1 (3.1)	5 (33.3)	6 (12.8)
Hyperbilirubinaemia	3 (9.4)	3 (20.0)	6 (12.8)
Neck pain	4 (12.5)	2 (13.3)	6 (12.8)
Pruritus	3 (9.4)	3 (20.0)	6 (12.8)
Asthenia	2 (6.3)	3 (20.0)	5 (10.6)
Blood alkaline phosphatase increased	2 (6.3)	3 (20.0)	5 (10.6)
Blood lactate dehydrogenase increased	4 (12.5)	1 (6.7)	5 (10.6)
Bone pain	4 (12.5)	1 (6.7)	5 (10.6)
Cellulitis	3 (9.4)	2 (13.3)	5 (10.6)
Febrile neutropenia	3 (9.4)	2 (13.3)	5 (10.6)
Fluid overload	4 (12.5)	1 (6.7)	5 (10.6)
Hyperkalaemia	5 (15.6)	0	5 (10.6)
Hyperphosphataemia	5 (15.6)	0	5 (10.6)
Leukocytosis	4 (12.5)	1 (6.7)	5 (10.6)
Leukopenia	2 (6.3)	3 (20.0)	5 (10.6)
Lymphopenia	3 (9.4)	2 (13.3)	5 (10.6)
Pain in extremity	3 (9.4)	2 (13.3)	5 (10.6)
Rash maculo-papular	3 (9.4)	2 (13.3)	5 (10.6)
Tumour lysis syndrome	2 (6.3)	3 (20.0)	5 (10.6)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event within a given PT, that patient was counted only once for that PT. If a patient experienced more than one event within a given system organ class, that patient was counted only once for that system organ class.
Source: Study 0114, Table 14.3.1.2B.

Adverse Events among Patients in the Summary of Clinical Safety Pool

Summaries of TEAEs and of common (i.e., incidence ≥10%) TEAEs among all patients in the SCS pool, regardless of indication, are summarised in Table 67 and Table 68, by MedDRA PT, sorted by overall incidence.

Table 67. Treatment-Emergent Adverse Events Summary: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study (Safety Population)

	Stemline-Sponsored Study				
Patients with at least 1:	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
TEAE	47 (100.0)	49 (100.0)	16 (100.0)	29 (100.0)	141 (100.0)
TEAE Related to Tagraxofusp	41 (87.2)	44 (89.8)	14 (87.5)	26 (89.7)	125 (88.7)
≥Grade 3 TEAE	38 (80.9)	43 (87.8)	11 (68.8)	27 (93.1)	119 (84.4)
≥Grade 3 TEAE Related to Tagraxofusp	30 (63.8)	28 (57.1)	9 (56.3)	16 (55.2)	83 (58.9)
SAE	23 (48.9)	33 (67.3)	8 (50.0)	17 (58.6)	81 (57.4)
SAE Related to Tagraxofusp	10 (21.3)	17 (34.7)	3 (18.8)	6 (20.7)	36 (25.5)
TEAE Leading to Discontinuation of Tagraxofusp	1 (2.1)	8 (16.3)	2 (12.5)	4 (13.8)	15 (10.6)
Tagraxofusp Related TEAE Leading to Discontinuation of Tagraxofusp	1 (2.1)	4 (8.2)	1 (6.3)	1 (3.4)	7 (5.0)
TEAE Occurring within 24 Hours of Dose	7 (14.9)	7 (14.3)	4 (25.0)	9 (31.0)	27 (19.1)
TEAE Leading to Dose Reduction	1 (2.1)	1 (2.0)	1 (6.3)	0	3 (2.1)
TEAE Leading to Dose Interruption	32 (68.1)	27 (55.1)	7 (43.8)	14 (48.3)	80 (56.7)
TEAE Leading to Death	3 (6.4)	8 (16.3)	0	5 (17.2)	16 (11.3)

Abbreviations: AML= acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: SCS Table 1.4.1.1.

Table 68. Most Common (≥10%) Treatment-Emergent Adverse Events: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study, by MedDRA Preferred Term (Safety Population)

	Stemline-Sponsored Study				
MedDRA Preferred Term	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
At least 1 TEAE	47 (100.0)	49 (100.0)	16 (100.0)	29 (100.0)	141 (100.0)
Alanine aminotransferase increased	30 (63.8)	31 (63.3)	7 (43.8)	9 (31.0)	77 (54.6)
Hypoalbuminaemia	26 (55.3)	30 (61.2)	8 (50.0)	13 (44.8)	77 (54.6)
Aspartate aminotransferase increased	28 (59.6)	34 (69.4)	6 (37.5)	4 (13.8)	72 (51.1)
Fatigue	21 (44.7)	27 (55.1)	7 (43.8)	15 (51.7)	70 (49.6)
Nausea	22 (46.8)	26 (53.1)	7 (43.8)	14 (48.3)	69 (48.9)
Oedema peripheral	24 (51.1)	19 (38.8)	4 (25.0)	15 (51.7)	62 (44.0)
Pyrexia	21 (44.7)	22 (44.9)	6 (37.5)	12 (41.4)	61 (43.3)
Thrombocytopenia	23 (48.9)	11 (22.4)	9 (56.3)	10 (34.5)	53 (37.6)
Dyspnoea	6 (12.8)	18 (36.7)	4 (25.0)	14 (48.3)	42 (29.8)
Headache	12 (25.5)	16 (32.7)	4 (25.0)	10 (34.5)	42 (29.8)
Chills	16 (34.0)	12 (24.5)	5 (31.3)	8 (27.6)	41 (29.1)
Hyperglycaemia	17 (36.2)	17 (34.7)	3 (18.8)	3 (10.3)	40 (28.4)
Anaemia	11 (23.4)	13 (26.5)	3 (18.8)	12 (41.4)	39 (27.7)
Decreased appetite	12 (25.5)	15 (30.6)	2 (12.5)	10 (34.5)	39 (27.7)
Weight increased	18 (38.3)	11 (22.4)	4 (25.0)	6 (20.7)	39 (27.7)
Hypotension	13 (27.7)	16 (32.7)	3 (18.8)	5 (17.2)	37 (26.2)
Vomiting	8 (17.0)	14 (28.6)	3 (18.8)	12 (41.4)	37 (26.2)
Dizziness	8 (17.0)	12 (24.5)	4 (25.0)	12 (41.4)	36 (25.5)
Constipation	11 (23.4)	10 (20.4)	2 (12.5)	12 (41.4)	35 (24.8)
Diarrhoea	8 (17.0)	13 (26.5)	3 (18.8)	10 (34.5)	34 (24.1)
Back pain	12 (25.5)	10 (20.4)	2 (12.5)	8 (27.6)	32 (22.7)
Hypokalaemia	10 (21.3)	11 (22.4)	1 (6.3)	7 (24.1)	29 (20.6)
Cough	3 (6.4)	13 (26.5)	2 (12.5)	10 (34.5)	28 (19.9)
Capillary leak syndrome	9 (19.1)	10 (20.4)	2 (12.5)	5 (17.2)	26 (18.4)
Insomnia	7 (14.9)	8 (16.3)	2 (12.5)	9 (31.0)	26 (18.4)
Febrile neutropenia	5 (10.6)	17 (34.7)	1 (6.3)	1 (3.4)	24 (17.0)
Tachycardia	7 (14.9)	10 (20.4)	3 (18.8)	4 (13.8)	24 (17.0)

MedDRA Preferred Term	Stemline-Sponsored Study				Total (N=141) n (%)
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	
Hypocalcaemia	11 (23.4)	8 (16.3)	1 (6.3)	3 (10.3)	23 (16.3)
Pain in extremity	5 (10.6)	8 (16.3)	1 (6.3)	7 (24.1)	21 (14.9)
Epistaxis	3 (6.4)	12 (24.5)	1 (6.3)	3 (10.3)	19 (13.5)
Hyponatraemia	9 (19.1)	7 (14.3)	1 (6.3)	2 (6.9)	19 (13.5)
Neutropenia	8 (17.0)	7 (14.3)	3 (18.8)	1 (3.4)	19 (13.5)
Anxiety	9 (19.1)	4 (8.2)	0	5 (17.2)	18 (12.8)
Abdominal pain	4 (8.5)	5 (10.2)	3 (18.8)	5 (17.2)	17 (12.1)
Hypertension	10 (21.3)	5 (10.2)	0	2 (6.9)	17 (12.1)
Myalgia	1 (2.1)	8 (16.3)	2 (12.5)	6 (20.7)	17 (12.1)
Blood alkaline phosphatase increased	5 (10.6)	9 (18.4)	1 (6.3)	1 (3.4)	16 (11.3)
Blood creatinine increased	6 (12.8)	6 (12.2)	2 (12.5)	1 (3.4)	15 (10.6)
Blood lactate dehydrogenase increased	5 (10.6)	8 (16.3)	2 (12.5)	0	15 (10.6)
Hypoxia	3 (6.4)	6 (12.2)	1 (6.3)	5 (17.2)	15 (10.6)
Leukocytosis	5 (10.6)	5 (10.2)	0	5 (17.2)	15 (10.6)
Oropharyngeal pain	7 (14.9)	4 (8.2)	1 (6.3)	3 (10.3)	15 (10.6)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Source: SCS Table 1.4.3.1.

A summary of TEAEs and common (ie, incidence ≥10%) TEAEs among all patients treated with tagraxofusp as a single agent at doses ≤12 μg/kg/day, regardless of indication, by dose is presented in Table 69 and Table 70 by MedDRA PT, sorted by overall incidence.

Table 69. Treatment-Emergent Adverse Events Summary: All Patients in the Summary of Clinical Safety Pool, Overall and by Tagraxofusp Dose (Safety Population)

Patients with at Least 1:	Tagraxofusp Dose			Total (N=134) n (%)
	7 μg/kg/day (N=12) n (%)	9 μg/kg/day (N=9) n (%)	12 μg/kg/day (N=113) n (%)	
TEAE	12 (100.0)	9 (100.0)	113 (100.0)	134 (100.0)
TEAE Related to Tagraxofusp	11 (91.7)	7 (77.8)	100 (88.5)	118 (88.1)
≥Grade 3 TEAE	10 (83.3)	5 (55.6)	97 (85.8)	112 (83.6)
≥Grade 3 TEAE Related to Tagraxofusp	8 (66.7)	4 (44.4)	66 (58.4)	78 (58.2)
SAE	6 (50.0)	4 (44.4)	64 (56.6)	74 (55.2)
SAE Related to Tagraxofusp	2 (16.7)	2 (22.2)	27 (23.9)	31 (23.1)
TEAE Leading to Discontinuation of Tagraxofusp	0	1 (11.1)	10 (8.8)	11 (8.2)
Tagraxofusp Related TEAE Leading to Discontinuation	0	0	4 (3.5)	4 (3.0)
TEAE Occurring within 24 Hours of Dose	1 (8.3)	1 (11.1)	23 (20.4)	25 (18.7)
TEAE Leading to Dose Reduction	0	0	3 (2.7)	3 (2.2)
TEAE Leading to Dose Interruption	3 (25.0)	2 (22.2)	72 (63.7)	77 (57.5)
TEAE Leading to Death	2 (16.7)	1 (11.1)	9 (8.0)	12 (9.0)

Abbreviations: R/R = relapsed/refractory; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: SCS Table 1.4.1.2.

Table 70. Most Common (≥10%) Treatment-Emergent Adverse Events: All Patients in the Summary of Clinical Safety Pool, Overall and by Tagraxofusp Dose, by MedDRA Preferred Term (Safety Population)

	Tagraxofusp Dose			
MedDRA Preferred Term	7 µg/kg/day (N=12) n (%)	9 µg/kg/day (N=9) n (%)	12 µg/kg/day (N=113) n (%)	Total (N=134) n (%)
Alanine aminotransferase increased	7 (58.3)	4 (44.4)	62 (54.9)	73 (54.5)
Hypoalbuminaemia	7 (58.3)	1 (11.1)	64 (56.6)	72 (53.7)
Aspartate aminotransferase increased	5 (41.7)	3 (33.3)	58 (51.3)	66 (49.3)
Fatigue	6 (50.0)	5 (55.6)	55 (48.7)	66 (49.3)
Nausea	7 (58.3)	1 (11.1)	58 (51.3)	66 (49.3)
Oedema peripheral	6 (50.0)	5 (55.6)	49 (43.4)	60 (44.8)
Pyrexia	5 (41.7)	2 (22.2)	50 (44.2)	57 (42.5)
Thrombocytopenia	6 (50.0)	2 (22.2)	42 (37.2)	50 (37.3)
Headache	3 (25.0)	5 (55.6)	33 (29.2)	41 (30.6)
Chills	3 (25.0)	0	37 (32.7)	40 (29.9)
Dyspnoea	4 (33.3)	5 (55.6)	30 (26.5)	39 (29.1)
Decreased appetite	3 (25.0)	1 (11.1)	34 (30.1)	38 (28.4)
Weight increased	1 (8.3)	3 (33.3)	33 (29.2)	37 (27.6)
Dizziness	4 (33.3)	2 (22.2)	30 (26.5)	36 (26.9)
Hyperglycaemia	4 (33.3)	4 (44.4)	28 (24.8)	36 (26.9)
Anaemia	5 (41.7)	1 (11.1)	29 (25.7)	35 (26.1)
Vomiting	4 (33.3)	2 (22.2)	29 (25.7)	35 (26.1)
Diarrhoea	3 (25.0)	4 (44.4)	27 (23.9)	34 (25.4)
Constipation	2 (16.7)	1 (11.1)	30 (26.5)	33 (24.6)
Hypotension	1 (8.3)	2 (22.2)	30 (26.5)	33 (24.6)
Back pain	2 (16.7)	3 (33.3)	26 (23.0)	31 (23.1)
Hypokalaemia	1 (8.3)	2 (22.2)	25 (22.1)	28 (20.9)
Cough	3 (25.0)	1 (11.1)	22 (19.5)	26 (19.4)
Insomnia	1 (8.3)	2 (22.2)	23 (20.4)	26 (19.4)
Capillary leak syndrome	1 (8.3)	2 (22.2)	20 (17.7)	23 (17.2)
Tachycardia	3 (25.0)	0	20 (17.7)	23 (17.2)
Febrile neutropenia	1 (8.3)	1 (11.1)	20 (17.7)	22 (16.4)
Hypocalcaemia	4 (33.3)	2 (22.2)	16 (14.2)	22 (16.4)
Pain in extremity	2 (16.7)	2 (22.2)	15 (13.3)	19 (14.2)

MedDRA Preferred Term	Tagraxofusp Dose 7 µg/kg/day (N=12) n (%)	9 µg/kg/day (N=9) n (%)	12 µg/kg/day (N=113) n (%)	Total (N=134) n (%)
Epistaxis	1 (8.3)	1 (11.1)	16 (14.2)	18 (13.4)
Anxiety	2 (16.7)	0	15 (13.3)	17 (12.7)
Hyponatraemia	3 (25.0)	1 (11.1)	13 (11.5)	17 (12.7)
Myalgia	2 (16.7)	4 (44.4)	11 (9.7)	17 (12.7)
Neutropenia	1 (8.3)	0	16 (14.2)	17 (12.7)
Abdominal pain	2 (16.7)	2 (22.2)	12 (10.6)	16 (11.9)
Hypertension	0	0	15 (13.3)	15 (11.2)
Leukocytosis	2 (16.7)	1 (11.1)	12 (10.6)	15 (11.2)
Hypomagnesaemia	2 (16.7)	1 (11.1)	11 (9.7)	14 (10.4)
Hypoxia	0	0	14 (12.4)	14 (10.4)
Oropharyngeal pain	0	0	14 (12.4)	14 (10.4)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Patients who received tagraxofusp at 16 µg/kg/day are not included in this table, as this dose level is above the intended to be marketed dose.
Source: SCS Table 1.4.3.2.

Table 71 Common TEAEs (>15%) Reported in First Line BPDCN Patients (12mcg/Kg/day) by Age-Study STML-401-0114

Preferred Term	Total N=66	Age Group <60 N=17	>60 to<65 N=9	>65-<75 N=29	>75 N=11
Alanine aminotransferase increased	44 (66.7)	14 (82.4)	7 (77.8)	17 (58.6)	6 (54.5)
Aspartate aminotransferase increased	40 (60.6)	12 (70.6)	7 (77.8)	15 (51.7)	6 (54.5)
Fatigue	28 (42.4)	9 (52.9)	3 (33.3)	13 (44.8)	3 (27.3)
Hypoalbuminaemia	28 (42.4)	6 (35.3)	1 (11.1)	17 (58.6)	4 (36.4)
Nausea	28 (42.4)	7 (41.2)	4 (44.4)	13 (44.8)	4 (36.4)
Pyrexia	27 (40.9)	10 (58.8)	3(33.3)	8 (27.6)	6 (54.5)
Thrombocytopenia	26 (39.4)	10 (58.8)	2 (22.2)	13 (44.8)	1 (9.1)
Weight increased	25 (37.9)	6 (35.3)	4 (44.4)	10 (34.5)	5 (45.5)
Headache	20 (30.3)	7 (41.2)	1 (11.1)	10 (34.5)	2 (18.1)
Hyperglycaemia	20 (30.3)	4 (23.5)	4 (44.4)	8 (27.6)	4 (36.4)
Oedema peripheral	20 (30.3)	3 (17.6)	1 (11.1)	11 (37.9)	5 (45.5)
Constipation	19 (28.8)	5 (29.4)	3(33.3)	9 (31.0)	2 (18.2)
Anaemia	15 (22.7)	6 (35.3)	0	8 (27.6)	1 (9.1)
Chills	14 (21.2)	6 (35.3)	2 (22.2)	5 (17.2)	1 (9.1)
Diarrhoea	14 (21.2)	4 (23.5)	2 (22.2)	7 (24.1)	1 (9.1)
Hypotension	14 (21.2)	3 (17.6)	1 (11.1)	7 (24.1)	3 (27.3)
Backpain	12 (18.2)	3 (17.6)	1 (11.1)	7 (24.1)	1 (9.1)
Hypokalaemia	12 (18.2)	4 (23.5)	0	7 (24.1)	1 (9.1)
Tachycardia	12 (18.2)	4 (23.5)	3(33.3)	3 (10.3)	2 (18.2)
Anxiety	11 (16.7)	6 (35.3)	2 (22.2)	3 (10.3)	0
Capillary leak syndrome	11 (16.7)	1 (5.9)	3(33.3)	5 (17.2)	2 (18.2)
Decreased appetite	11 (16.7)	2 (11.8)	1 (11.1)	7 (24.1)	1(9.1)
Dizziness	11 (16.7)	3 (17.6)	1 (11.1)	6 (20.7)	1(9.1)
Hyperphosphatemia	11 (16.7)	4 (23.5)	2 (22.2)	3 (10.2)	2 (18.2)

Table 72 provides TEAEs reported in ≥10% of patients in the SCS pool, by cycle of onset and grade.

Table 72. Most Common (≥10% of Patients) Treatment-Emergent Adverse Events: All Patients in the Summary of Clinical Safety Pool, Overall and by Grade and by Cycle, by MedDRA Preferred Term (Safety Population)

	Cycle 1 & Cycle 2 N=141 n (%)		Cycles 3 & Beyond N=73 n (%)		
MedDRA Preferred Term	Any Intensity	≥Grade 3 Intensity	Any Intensity	≥Grade 3 Intensity	Overall Incidence
Alanine aminotransferase increased	76 (53.9)	35 (24.8)	5 (6.8)	1 (1.4)	77 (54.6)
Hypoalbuminaemia	75 (53.2)	1 (0.7)	7 (9.6)	0	77 (54.6)
Aspartate aminotransferase increased	71 (50.4)	34 (24.1)	3 (4.1)	0	72 (51.1)
Fatigue	60 (42.6)	6 (4.3)	18 (24.7)	3 (4.1)	70 (49.6)
Nausea	64 (45.4)	1 (0.7)	13 (17.8)	0	69 (48.9)
Oedema peripheral	55 (39.0)	1 (0.7)	12 (16.4)	0	62 (44.0)
Pyrexia	57 (40.4)	1 (0.7)	9 (12.3)	1 (1.4)	61 (43.3)
Thrombocytopenia	52 (36.9)	42 (29.8)	5 (6.8)	3 (4.1)	53 (37.6)
Dyspnoea	39 (27.7)	2 (1.4)	7 (9.6)	2 (2.7)	42 (29.8)
Headache	38 (27.0)	0	8 (11.0)	0	42 (29.8)
Chills	37 (26.2)	1 (0.7)	6 (8.2)	0	41 (29.1)
Hyperglycaemia	37 (26.2)	11 (7.8)	12 (16.4)	4 (5.5)	40 (28.4)
Anaemia	36 (25.5)	26 (18.4)	8 (11.0)	5 (6.8)	39 (27.7)
Decreased appetite	33 (23.4)	0	8 (11.0)	1 (1.4)	39 (27.7)
Weight increased	33 (23.4)	0	11 (15.1)	0	39 (27.7)
Hypotension	30 (21.3)	9 (6.4)	10 (13.7)	2 (2.7)	37 (26.2)
Vomiting	33 (23.4)	1 (0.7)	5 (6.8)	0	37 (26.2)
Dizziness	26 (18.4)	0	13 (17.8)	1 (1.4)	36 (25.5)
Constipation	32 (22.7)	0	7 (9.6)	0	35 (24.8)
Diarrhoea	25 (17.7)	0	14 (19.2)	2 (2.7)	34 (24.1)
Back pain	21 (14.9)	0	13 (17.8)	2 (2.7)	32 (22.7)
Hypokalaemia	28 (19.9)	1 (0.7)	4 (5.5)	2 (2.7)	29 (20.6)
Cough	20 (14.2)	0	8 (11.0)	0	28 (19.9)
Capillary leak syndrome	26 (18.4)	9 (6.4)	0	0	26 (18.4)
Insomnia	24 (17.0)	0	4 (5.5)	0	26 (18.4)
Febrile neutropenia	22 (15.6)	19 (13.5)	4 (5.5)	3 (4.1)	24 (17.0)
Tachycardia	21 (14.9)	0	4 (5.5)	0	24 (17.0)

Tagraxofusp-related Adverse Events among All Patients in the Summary of Clinical Safety Pool

Tagraxofusp-related TEAEs, as assessed by the Investigator, occurring in >5% of patients in the SCS pool are summarised by MedDRA PT in Table 73.

Table 73. Tagraxofusp-Related TEAEs (as Assessed by the Investigator) Occurring in >5% of Patients: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study, by MedDRA Preferred Term (Safety Population)

	Stemline-Sponsored Study				
MedDRA Preferred Term	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
At Least 1 Treatment-Related TEAE	41 (87.2)	44 (89.8)	14 (87.5)	26 (89.7)	125 (88.7)
Hypoalbuminaemia	24 (51.1)	26 (53.1)	8 (50.0)	10 (34.5)	68 (48.2)
Alanine aminotransferase increased	24 (51.1)	29 (59.2)	6 (37.5)	6 (20.7)	65 (46.1)
Aspartate aminotransferase increased	24 (51.1)	30 (61.2)	6 (37.5)	4 (13.8)	64 (45.4)
Thrombocytopenia	17 (36.2)	7 (14.3)	7 (43.8)	9 (31.0)	40 (28.4)
Nausea	11 (23.5)	15 (30.6)	5 (31.3)	8 (27.6)	39 (27.7)
Fatigue	9 (19.1)	15 (30.6)	3 (18.8)	8 (27.6)	35 (24.8)
Pyrexia	14 (29.8)	13 (26.5)	5 (31.3)	3 (10.3)	35 (24.8)
Weight increased	13 (27.7)	8 (16.3)	3 (18.8)	3 (10.3)	27 (19.1)
Chills	13 (27.7)	6 (12.2)	4 (25.0)	3 (10.3)	26 (18.4)
Capillary leak syndrome	9 (19.1)	10 (20.4)	2 (12.5)	5 (17.2)	26 (18.4)
Oedema peripheral	8 (17.0)	10 (20.4)	2 (12.5)	5 (17.2)	25 (17.7)
Hypotension	7 (14.9)	12 (24.5)	2 (12.5)	3 (10.3)	24 (17.0)
Vomiting	2 (4.3)	9 (18.4)	3 (18.8)	7 (24.1)	21 (14.9)
Anaemia	6 (12.8)	6 (12.2)	2 (12.5)	5 (17.2)	19 (13.5)
Decreased appetite	7 (14.9)	5 (10.2)	1 (6.3)	2 (6.9)	15 (10.6)
Blood alkaline phosphatase increased	3 (6.4)	8 (16.3)	1 (6.3)	1 (3.4)	13 (9.2)
Neutropenia	5 (10.6)	4 (8.2)	2 (12.5)	1 (3.4)	12 (8.5)
Back pain	6 (12.8)	2 (4.1)	0	4 (13.8)	12 (8.5)
Headache	1 (2.1)	2 (4.1)	1 (6.3)	4 (13.8)	8 (5.7)
Leukopenia	4 (8.5)	3 (6.1)	0	1 (3.4)	8 (5.7)
Tachycardia	4 (8.5)	1 (2.0)	2 (12.5)	1 (3.4)	8 (5.7)
Dyspnoea	1 (2.1)	2 (4.1)	2 (12.5)	3 (10.3)	8 (5.7)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT. If a patient experienced more than one event within a given system organ class, that patient was counted only once for that system organ class. Adverse events with missing relationships were considered related.
Source: SCS, Table 1.4.5.1.

Grade 3 or Greater Adverse Events Among All Patients in the Summary of Clinical Safety Pool

A summary of ≥Grade 3 TEAEs reported for >5% of patients in the SCS pool, by MedDRA SOC and PT, is presented in Table 74, overall and by indication/study.

Table 74. Grade 3 or Greater Treatment-Emergent Adverse Events Reported for >5% of Patients: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study, by MedDRA SOC and Preferred Term (Safety Population)

MedDRA System Organ Class / Preferred Term	Stemline-Sponsored Study				
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
At Least 1 TEAE with CTCAE ≥Grade 3	38 (80.9)	43 (87.8)	11 (68.8)	27 (93.1)	119 (84.4)
Blood and lymphatic system disorders	22 (46.8)	32 (65.3)	9 (56.3)	19 (65.5)	82 (58.2)
Anaemia	5 (10.6)	11 (22.4)	2 (12.5)	10 (34.5)	28 (19.9)
Febrile neutropenia	4 (8.5)	15 (30.6)	1 (6.3)	1 (3.4)	21 (14.9)
Leukocytosis	1 (2.1)	4 (8.2)	0	5 (17.2)	10 (7.1)
Leukopenia	4 (8.5)	5 (10.2)	0	2 (6.9)	11 (7.8)
Lymphopenia	3 (6.4)	3 (6.1)	1 (6.3)	0	7 (5.0)
Neutropenia	5 (10.6)	5 (10.2)	2 (12.5)	1 (3.4)	13 (9.2)
Thrombocytopenia	19 (40.4)	11 (22.4)	6 (37.5)	8 (27.6)	44 (31.2)
General disorders and administration site conditions	4 (8.5)	9 (18.4)	0	5 (17.2)	18 (12.8)
Fatigue	3 (6.4)	4 (8.2)	0	2 (6.9)	9 (6.4)
Infections and infestations	3 (6.4)	12 (24.5)	1 (6.3)	8 (27.6)	24 (17.0)
Pneumonia	2 (4.3)	5 (10.2)	0	0	7 (5.0)
Investigations	24 (51.1)	19 (38.8)	6 (37.5)	1 (3.4)	50 (35.5)
Alanine aminotransferase increased	17 (36.2)	12 (24.5)	5 (31.3)	1 (3.4)	35 (24.8)
Aspartate aminotransferase increased	16 (34.0)	14 (28.6)	4 (25.0)	0	34 (24.1)
Metabolism and nutrition disorders	21 (44.7)	11 (22.4)	1 (6.3)	9 (31.0)	42 (29.8)
Hyperglycaemia	7 (14.9)	3 (6.1)	1 (6.3)	2 (6.9)	13 (9.2)
Hyponatraemia	6 (12.8)	1 (2.0)	0	2 (6.9)	9 (6.4)
Hypophosphataemia	4 (8.5)	3 (6.1)	0	1 (3.4)	8 (5.7)
Tumour lysis syndrome	5 (10.6)	2 (4.1)	0	3 (10.3)	10 (7.1)
Respiratory, thoracic and mediastinal disorders	3 (6.4)	8 (16.3)	1 (6.3)	6 (20.7)	18 (12.8)
Respiratory failure	2 (4.3)	4 (8.2)	0	1 (3.4)	7 (5.0)
Vascular disorders	10 (21.3)	9 (18.4)	2 (12.5)	6 (20.7)	27 (19.1)
Capillary leak syndrome	3 (6.4)	3 (6.1)	2 (12.5)	1 (3.4)	9 (6.4)
Hypertension	5 (10.6)	2 (4.1)	0	2 (6.9)	9 (6.4)
Hypotension	4 (8.5)	4 (8.2)	0	2 (6.9)	10 (7.1)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT. If a patient experienced more than one event within a given SOC, that patient was counted only once for that system organ class. Adverse events with missing relationships were considered related.
Source: SCS Table 1.4.8.1.

Common Adverse Events of Interest

Liver Transaminase Elevations

Patients with BPDCN in Study 0114

ALT increased and AST increased were the most common TEAEs among BPDCN patients (N=47). A summary of TEAEs representing liver transaminase elevations in BPDCN patients is presented in Table 75, overall and by line of therapy.

Table 75. Summary of Elevated Liver Transaminase TEAEs: First-Line and R/R BPDCN Patients in Study 0114, Overall and by Line of Therapy (Safety Population)

	Disease		
MedDRA Preferred Term	First-Line BPDCN Patients (N=32) n (%)	R/R BPDCN Patients (N=15) n (%)	Total BPDCN Patients (N=47) n (%)
Alanine aminotransferase increased	22 (68.8)	8 (53.3)	30 (63.8)
Aspartate aminotransferase increased	21 (65.6)	7 (46.7)	28 (59.6)
Liver function test increased	3 (9.4)	1 (6.7)	4 (8.5)
Transaminase increased	0	1 (6.7)	1 (2.1)
Hepatic enzyme increased	0	0	0

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed/refractory.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Adverse events were coded using MedDRA version 19.0.
Source: Study 0114, Table 14.3.1.2B.

A summary of the incidence of ALT increased and AST increased among BPDCN patients, including relationship, severity, seriousness and treatment discontinuation incidence, is presented in Table 76.

Table 76. Incidence of ALT Increased and AST Increased: First-Line and R/R BPDCN Patients, Overall and by Relationship to Tagraxofusp, Severity, Seriousness, and Discontinuation of Treatment (Safety Population)

MedDRA Preferred Term/ Disease	Any TEAEs n (%)	Tagraxofusp-Related n (%)	Grade 3 n (%)	Grade 4 n (%)	Serious n (%)	Led to Tagraxofusp Discon-tinuation n (%)
ALT Increased						
First-line BPDCN (N=32)	22 (68.8)	18 (56.3)	12 (37.5)	0	0	0
R/R BPDCN (N=15)	8 (53.3)	6 (40.0)	5 (33.3)	0	1 (6.7)	0
All BPDCN (N=47)	30 (63.8)	24 (51.1)	17 (36.2)	0	1 (2.1)	0
AST Increased						
First-line BPDCN (N=32)	21 (65.6)	18 (56.3)	10 (31.3)	0	0	0
R/R BPDCN (N=15)	7 (46.7)	6 (40.0)	6 (40.0)	1 (6.7)	2 (13.3)	0
All BPDCN (N=47)	28 (59.6)	24 (51.1)	16 (34.0)	1 (2.1)	2 (4.3)	0

Abbreviations: ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = Treatment-Emergent Adverse Event.
Adverse events were coded using MedDRA version 19.0.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Adverse events with missing relationship were considered related.
Source: Study 0114, Listing 16.2.7.1 and Table 14.3.1.2B, Table 14.3.1.4B, Table 14.3.2.4, Table 14.3.1.7B and Table 14.3.1.8B.

The most BPDCN patients who experienced ALT and AST increase did so in C1, with a notably lower incidence thereafter.

All Patients in the Summary of Clinical Safety Pool

Findings for TEAEs related to liver transaminase elevations among all 141 patients in the SCS pool were generally similar to those among BPDCN patients, with ALT increased (55% [77/141]) and AST increased (51% [72/141]) being the most common TEAEs overall and treatment-related TEAEs overall

(46% [65/141] and 45% [64/141], respectively). The Grade 3 incidence of these events was 25% (35/141) and 24% (34/141), respectively.

Capillary Leak Syndrome

CLS is an identified risk with tagraxofusp. A summary of CLS TEAEs based on MedDRA preferred term reported among all patients in the SCS pool is presented in Table 77, overall and by indication/study.

All Patients in the Summary of Clinical Safety Pool

Table 77. Summary of Capillary Leak Syndrome Events: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study (Safety Population)

	Stemline-Sponsored Study				
MedDRA Preferred Term	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
At Least One CLS Event, n (%)	9 (19.1)	10 (20.4)	2 (12.5)	5 (17.2)	26 (18.4)
Total Number of CLS Events, n	9	10	3	5	27
Resolved CLS Events, n (%)[1]	7 (77.8)	7 (70.0)	3 (100.0)	5 (100.0)	22 (81.5)
Ongoing CLS Events, n (%)[1]	0	2 (20.0)	0	0	2 (7.4)
CLS Events Leading to Death, n (%)[1]	2 (22.2)	1 (10.0)	0	0	3 (11.1)
Received Albumin Infusion, n (%)[2,3]	9 (19.1)	10 (20.4)	--	--	19 (19.8)
Time to First Albumin Infusion (days)[4]					
Mean (StD)	1.2 (1.30)	0.2 (1.69)	--	--	0.7 (1.57)
Median	2.0	1.0	--	--	1.0
Min, Max	-1, 2	-3, 1	--	--	-3, 2
At Least One CLS Event, n (%)[3]	9 (19.1)	10 (20.4)	2 (12.5)	5 (17.2)	26 (18.4)
Grade 3 CLS	0	1 (2.0)	2 (12.5)	1 (3.4)	4 (2.8)
Grade 4 CLS	1 (2.1)	1 (2.0)	0	0	2 (1.4)
Grade 5 CLS	2 (4.3)	1 (2.0)	0	0	3 (2.1)

MedDRA Preferred Term	Stemline-Sponsored Study				
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
Any Recurring CLS, n (%)	0	0	1 (6.3)	0	1 (0.7)
Time to Any CLS Event (days)					
Mean (StD)	10.7 (15.25)	7.7 (7.65)	17.0 (21.17)	5.8 (2.28)	9.4 (11.74)
Median	5.0	5.0	9.0	6.0	5.0
Min, Max	4, 51	4, 29	1, 41	2, 8	1, 51
Time to Resolution of CLS Event (days)					
Mean (StD)	6.9 (5.70)	9.0 (8.47)	3.7 (0.58)	9.0 (1.58)	7.6 (5.81)
Median	4.0	6.0	4.0	9.0	6.0
Min, Max	3, 19	4, 28	3, 4	7, 11	3, 28
Time to Recurrence of CLS (days)					
Mean (StD)	0	0	41.0 (NA)	0	41.0 (NA)
Median			41.0		41.0
Min, Max			41, 41		41, 41
Time to Grade ≥3 CLS (days)					
Mean (StD)	7.0 (2.65)	4.3 (0.58)	25.0 (22.63)	8.0 (NA)	10.2 (11.74)
Median	8.0	4.0	25.0	8.0	8.0
Min, Max	4, 9	4, 5	9, 41	8, 8	4, 41
Time to Resolution of ≥Grade 3 CLS (days)					
Mean (StD)	9.0 (NA)	6.0 (2.83)	3.5 (0.71)	7.0 (NA)	5.8 (2.48)
Median	9.0	6.0	3.5	7.0	5.5
Min, Max	9, 9	4, 8	3, 4	7, 7	3, 9
Time to Recurrence of ≥Grade 3 CLS (days)					
Mean (StD)	0	0	41.0 (NA)	0	41.0 (NA)
Median			41.0		41.0
Min, Max			41, 41		41, 41

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CLS = capillary leak syndrome; Max = maximum; Min = Minimum; StD = standard deviation.
1 At the time of data cutoff. Denominator was based on the total number of CLS events.
2 Data reported for Study 0114 only (N=96)

CLS was Grade 3 and Grade 4 in intensity for 4 and 2 patients, respectively. For 3 patients, 2 with BPDCN and 1 with AML, CLS was Grade 5. One patient discontinued tagraxofusp because of CLS. Of the 22 patients who continued treatment beyond C1, only 1 patient experienced a recurrence of CLS when retreated with tagraxofusp. This patient was enrolled in Study 0214, experienced Grade 2 CLS in C1 and then experienced a recurrence of CLS in C2, with the latter event assessed as Grade 3 and serious. Tagraxofusp was interrupted, and the event resolved in both cases.

After the occurrence of a case of Grade 5 CLS during the dose-escalation phase of Study 0114 in a patient in the 7 µg/kg/day cohort, the protocol was amended (Amendment 6) to provide risk mitigation strategies for CLS. The incidence of ≥Grade 3 CLS before implementation of these changes was 17% (1/6 patients) and after implementation was 6% (8/135 patients). Furthermore, the rate of Grade 5 CLS in particular decreased from 17% (1/6) before implementation of these changes to 1.5% (2/135) after implementation.

Additional analyses were conducted on the data across all 96 patients in Study 0114. Findings revealed no notable differences in these categories of patients by sex, age, medical history, baseline disease burden or number of doses in C1.

In Study 0114, all 19 patients who experienced CLS received IV albumin, with the median time to the first albumin infusion after initiating tagraxofusp being 1 day and a maximum time of 2 days.

Review of laboratory data among patients with CLS in Study 0114 revealed an apparent downward trend in albumin levels over the 5-day period before the onset of CLS.

CLS represents a constellation of symptoms that may occur concurrently or sequentially. Common signs and symptoms (incidence ≥ 20%) associated with these potential CLS cases that were reported during treatment with tagraxofusp include hypoalbuminaemia, oedema, weight gain, and hypotension.

Hypoalbuminaemia

Patients with BPDCN in Study 0114

The overall incidence of potential CLS cases among the 81 patients who received 12 µg/kg/day tagraxofusp in Study 0114 was 54% (44 of 81 patients). Most cases (38 of 44, 86%) were Grade 1 or 2 in severity. Grade 3 potential CLS events were reported in 4 patients (5%), Grade 4 in 1 patient (1%), and Grade 5 in 2 patients (2%).

The incidence of hypoalbuminaemia among BPDCN patients is summarised in Table 78.

Of note, 1 BPDCN patient discontinued tagraxofusp because of hypoalbuminaemia in the setting of CLS, with the latter event being fatal.

Table 78. Incidence of Hypoalbuminaemia: First-Line and R/R BPDCN Patients in Study 0114, Overall and by Relationship to Tagraxofusp, Severity, Seriousness, and Discontinuation of Treatment (Safety Population)

	Hypoalbuminaemia				
Disease	Any TEAEs n (%)	Tagraxofusp - Related n (%)	≥Grade 3 n (%)	Serious n (%)	Led to Tagraxofusp Discon-tinuation n (%)
First-line BPDCN (N=32)	14 (43.8)	12 (37.5)	0	0	1 (3.1)
R/R BPDCN (N=15)	12 (80.0)	12 (80.0)	0	0	0
All BPDCN (N=47)	26 (55.3)	24 (51.1)	0	0	1 (2.1)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; PT = preferred term; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA version 19.0.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Adverse events with missing relationship were considered related.
Source: Study 0114, Table 14.3.1.13.2B and Table 14.3.1.13.3.

Overall, hypoalbuminaemia occurred early during treatment, with a median time to first onset of 4 days. The incidence of hypoalbuminaemia was notably higher in C1 than in C2 through C4, with none of the BPDCN patients experiencing hypoalbuminaemia after C4.

All Patients in the Summary of Clinical Safety Pool

Findings for hypoalbuminaemia among all 141 patients in the SCS pool were similar to those among BPDCN patients. Overall, the incidence of hypoalbuminaemia was 55% (77/141) and of treatment-related hypoalbuminaemia was 48% (68/141); thus, hypoalbuminaemia was considered treatment-related for 68 of 77 patients who experienced it. Most patients who experienced hypoalbuminaemia did so in C1 or C2, with a notable decline in the incidence of this event thereafter.

Oedema

Patients with BPDCN in Study 0114

The incidence of oedema events is summarised in Table 79 for all BPDCN patients, regardless of tagraxofusp dose.

Oedema events were considered related to tagraxofusp for 8 of 24 patients. All but 1 oedema event were Grade 1 or 2 in intensity. For most (30 of 32) patients who experienced an oedema event, no concurrent weight increase was reported. None led to treatment discontinuation. Incidence was higher at cycle 1 and lower thereafter.

Table 79. Oedema Events: First-line and R/R BPDCN Patients in Study 0114, Overall and by Disease and Line of Therapy, Overall and by Relationship to Study Drug, Severity, Seriousness, and Discontinuation of Treatment (Safety Population)

	Oedema Events				
Disease	Any TEAEs n (%)	Tagraxofusp-Related n (%)	Grade 3 n (%)	Serious n (%)	Led to Tagraxofusp Discon-tinuation n (%)
First-line BPDCN (N=32)	13 (40.6)	5 (15.6)	0	0	0
R/R BPDCN (N=15)	11 (73.3)	3 (20.0)	1 (6.7)	0	0
All BPDCN Patients (N=47)	24 (51.1)	8 (17.0)	1 (2.1)	0	0

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; PT = preferred term; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA version 19.0.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Adverse events with missing relationship were considered related.
Source: Study 0114, Table 14.3.1.13.2B and Table 14.3.1.13.3.

An analysis of oedema events was not done specifically for all 141 patients in the SCS pool.

Weight Increased

Patients with BPDCN in Study 0114

Overall, 38% (18/47) of BPDCN patients experienced the TEAE weight increased, with a slightly higher incidence in first-line BPDCN patients (41% [13/32]) than in R/R BPDCN patients (33% [5/15]). All cases of weight increased were Grade 1 or 2 in intensity and non-serious and none led to tagraxofusp discontinuation. The incidence of weight increased was highest in C1 (26% [12/47]), with lower incidences thereafter.

All Patients in the Summary of Clinical Safety Pool

Overall, the incidence of weight increased was 28% (39/141). All cases of weight increased were Grade 1 or 2 in intensity and nonserious.

Hypotension

Patients with BPDCN in Study 0114

Overall, 32% (13/47) of BPDCN patients experienced the TEAE of hypotension, with a higher incidence in R/R BPDCN patients (40% [6/15]) than in first-line BPDCN patients (22% [7/32]). Most cases of hypotension were Grade 1 or 2 in intensity; in 4 patients (9%) hypotension was Grade 3, including 1 patient in which the event was serious in nature.

All Patients in the Summary of Clinical Safety Pool

Overall, the incidence of hypotension was 26% (37/141). Most cases were Grade 1 or 2 in intensity; 10 patients (7%) had Grade 3 (9 patients) or Grade 4 (1 patient) hypotension reported as a TEAE. Two patients had hypotension reported as an SAE and 1 patient withdrew from treatment due to hypotension. Most patients who experienced hypotension did so in C1 or C2, with a lower incidence of this event thereafter.

Haematologic TEAEs

Patients with BPDCN in Study 0114

A summary of common (i.e., incidence ≥10%) haematologic TEAEs is presented in Table 80, overall among BPDCN patients and by line of therapy.

Table 80. Summary of Common (i.e., Overall Incidence ≥10%) Haematologic TEAEs: First-line and R/R BPDCN Patients in Study 0114, Overall and by Line of Therapy (Safety Population)

MedDRA SOC / Preferred Term	Disease: First-Line BPDCN Patients (N=32) n (%)	Disease: R/R BPDCN Patients (N=15) n (%)	Total BPDCN Patients (N=47) n (%)
Blood and lymphatic system disorders	22 (68.8)	10 (66.7)	32 (68.1)
Thrombocytopenia	16 (50.0)	7 (46.7)	23 (48.9)
Anaemia	8 (25.0)	3 (20.0)	11 (23.4)
Neutropenia	3 (9.4)	5 (33.3)	8 (17.0)
Febrile neutropenia	3 (9.4)	2 (13.3)	5 (10.6)
Leukocytosis	4 (12.5)	1 (6.7)	5 (10.6)
Leukopenia	2 (6.3)	3 (20.0)	5 (10.6)
Lymphopenia	3 (9.4)	2 (13.3)	5 (10.6)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed/refractory; SOC = system organ class.
Adverse events were coded using MedDRA version 19.0.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Source: Study 0114, Table 14.3.1.2B.

Review of time to onset of these common haematologic TEAEs showed that most patients who experienced thrombocytopenia and anaemia did so in C1; ≤4 patients experienced thrombocytopenia in any given cycle after C1 and ≤2 patients experienced anaemia in any given cycle after C1. A different pattern was seen for neutropenia, with a higher incidence seen in C2 to C4 than in C1. The incidence of leukocytosis was relatively low and similar across cycles.

A summary of common haematologic TEAEs among BPDCN patients is presented in Table 81.

Table 81. Incidence of Common (i.e., Incidence ≥20%) Haematologic TEAEs: First-line and R/R BPDCN Patients in Study 0114, Overall and by Relationship to Tagraxofusp, Severity, Seriousness, and Discontinuation of Treatment (Safety Population)

MedDRA Preferred Term/ Disease	Any TEAE n (%)	Tagraxofusp Related n (%)	Grade 3 n (%)	Grade 4 n (%)	Serious n (%)	Led to Tagraxofusp Discon-tinuation n (%)
Thrombocytopenia						
First-line BPDCN (N=32)	16 (50.0)	11 (34.4)	10 (31.3)	6 (18.8)	0	0
R/R BPDCN (N=15)	7 (46.7)	6 (40.0)	5 (33.3)	6 (40.0)	1 (6.7)	0
All Patients (N=47)	23 (48.9)	17 (36.2)	15 (31.9)	12 (25.5)	1 (2.1)	0
Anaemia						
First-line BPDCN (N=32)	8 (25.0)	4 (12.5)	3 (9.4)	0	0	0
R/R BPDCN (N=15)	3 (20.0)	2 (13.3)	2 (13.3)	0	0	0
All Patients (N=47)	11 (23.4)	6 (12.8)	5 (10.6)	0	0	0

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA version 19.0.
If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Adverse events with missing relationship were considered related.
Source: Study 0114, Listing 16.2.7.1 and Table 14.3.1.2B, Table 14.3.1.4B, Table 14.3.2.4, Table 14.3.1.7B and Table 14.3.1.8B.

All Patients in the Summary of Clinical Safety Pool

Findings for haematologic TEAEs among all 141 patients in the SCS pool were similar to those among BPDCN patients; the incidences of thrombocytopenia, anaemia, and neutropenia were 38% (53/141), 28% (39/141), and 14% (19/141), respectively. The Grade 3/4 incidence of thrombocytopenia was 31% (44/141), with 32 of these patients experiencing Grade 4 thrombocytopenia. Twenty-eight (20%) patients experienced Grade 3 anaemia; 1 patient reported a Grade 4 event. Thirteen (9%) patients experienced Grade 3/4 neutropenia, with 11 patients experiencing Grade 4 neutropenia. All but 2 of these common haematologic TEAEs were non serious; 1 BPDCN patient experienced serious

thrombocytopenia. One patient in Study 0314 discontinued treatment with tagraxofusp due to a haematologic TEAE, leukocytosis. Most patients who experienced thrombocytopenia did so in C1, with a notable decline in the incidence of such events thereafter, even with continued therapy. The incidence of anaemia and neutropenia changed only slightly from C1 (23% [32/141] and 9% [13/141], respectively) to C2 to C4 (8% [11/141] and 8% [11/141], respectively). Four patients (3%) experienced anaemia and 1 patient experienced neutropenia after C4, indicating cumulative haematologic toxicity is not seen with tagraxofusp.

Other significant events

Infusion-Related Reactions

Patients with BPDCN in Study 0114

In Study 0114, a medical review of AE terms was performed to identify TEAEs considered representative of potential IRRs; such events are presented in Table 82 for BPDCN patients, overall and by line of therapy, by MedDRA PT.

Table 82. TEAEs Considered Representative of Infusion-related Reactions: First-line and R/R BPDCN Patients, Overall and by Line of Therapy, by MedDRA Preferred Term (Safety Population)

	Disease		
MedDRA Preferred Term	First-Line BPDCN Patients (N=32) n (%)	R/R BPDCN Patients (N=15) n (%)	Total BPDCN Patients (N=47) n (%)
At Least 1 Infusion-related reaction	5 (15.6)	2 (13.3)	7 (14.9)
Chills	2 (6.3)	1 (6.7)	3 (6.4)
Infusion-related reaction[1]	1 (3.1)	1 (6.7)	2 (4.3)
Back pain	2 (6.3)	0	2 (4.3)
Hypotension	1 (3.1)	1 (6.7)	2 (4.3)
Flushing	1 (3.1)	0	1 (2.1)
Bone pain	1 (3.1)	0	1 (2.1)

Abbreviations: BPDCN = blastic plasmacytoid dendritic cell neoplasm; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Note: Infusion-related reactions were defined as adverse events occurring within 24 hours of infusion.
1 For 1 patient, the IRR was characterised by tachycardia, tachypnea, exertional dyspnoea, hypotension, and pyrexia. For the second patient, the IRR was characterised by bilateral back pain.

Overall, 15% (7/47) of BPDCN patients experienced TEAEs considered representative of an IRR.

One patient (first-line BPDCN) experienced angioedema on C1D5, an SAE. The event was characterised by tongue swelling and difficulty speaking, and tagraxofusp was interrupted. The patient was hospitalised and received treatment with diphenhydramine, methylprednisolone, prednisone, cetirizine, and chlorhexidine, and the event resolved 9 days after onset. The Investigator considered this event to be Grade 3 in intensity and tagraxofusp related, although potentially related to the combined effects of tagraxofusp and a concomitant angiotensin converting enzyme inhibitor (enalapril). The patient continued tagraxofusp despite this event, with no recurrence with continued treatment.

Review of the incidence of the specific MedDRA PT "infusion-related reaction" showed that in addition to the 2 BPDCN patients who experienced the TEAE IRR, 2 AML patients in Study 0114 experienced the TEAE IRR; thus, the incidence of this event in the SCS pool was 3% (4/141). This event was Grade 3 in intensity and serious for 2 patients, with the event leading to tagraxofusp discontinuation for 1 of these 2 patients. This event was assessed by the Investigator as tagraxofusp-related for all 4 patients.

Hypersensitivity Reactions

All Patients in the Summary of Clinical Safety Pool

Analysis of the SMQ "Hypersensitivity" showed among all 141 patients in the SCS pool that 68 (48%) experienced at least 1 TEAE related to hypersensitivity; a summary of such events reported for >1 patient is presented in Table 83.

Table 83. Treatment-Emergent Adverse Events Related to Hypersensitivity Reported for >1 Patient Overall, Based on the SMQ "Hypersensitivity," All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study (Safety Population)

	Stemline-Sponsored Study				
MedDRA Preferred Term	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
SMQ Hypersensitivity	23 (48.9)	22 (44.9)	6 (37.5)	17 (58.6)	68 (48.2)
Pruritus	6 (12.8)	4 (8.2)	1 (6.3)	2 (6.9)	13 (9.2)
Rash	4 (8.5)	4 (8.2)	1 (6.3)	4 (13.8)	13 (9.2)
Stomatitis	4 (8.5)	5 (10.2)	0	3 (10.3)	12 (8.5)
Flushing	1 (2.1)	4 (8.2)	1 (6.3)	5 (17.2)	11 (7.8)
Rash maculo-papular	5 (10.6)	2 (4.1)	0	2 (6.9)	9 (6.4)
Respiratory failure	2 (4.3)	4 (8.2)	0	1 (3.4)	7 (5.0)
Erythema	3 (6.4)	2 (4.1)	0	1 (3.4)	6 (4.3)
Wheezing	1 (2.1)	3 (6.1)	0	0	4 (2.8)
Pneumonitis	0	1 (2.0)	1 (6.3)	1 (3.4)	3 (2.1)
Rash erythematous	0	1 (2.0)	1 (6.3)	1 (3.4)	3 (2.1)
Rash macular	1 (2.1)	1 (2.0)	0	1 (3.4)	3 (2.1)
Acute respiratory failure	1 (2.1)	1 (2.0)	0	0	2 (1.4)
Cytokine release syndrome	2 (4.3)	0	0	0	2 (1.4)
Dermatitis contact	0	1 (2.0	1 (6.3)	0	2 (1.4)
Drug hypersensitivity	0	1 (2.0)	1 (6.3)	0	2 (1.4)

MedDRA Preferred Term	Stemline-Sponsored Study				
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
Erythema multiforme	0	1 (2.0)	1 (6.3)	0	2 (1.4)
Generalised oedema	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Periorbital oedema	0	1 (2.0)	1 (6.3)	0	2 (1.4)
Swelling face	2 (4.3)	0	0	0	2 (1.4)
Urticaria	0	2 (4.1)	0	0	2 (1.4)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardised MedDRA Query
Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT.
Source: SCS Table 1.4.14.1.

Most hypersensitivity events were Grade 1 or 2 in intensity and nonserious. Thirteen (9%) patients experienced a ≥Grade 3 hypersensitivity event, including 2 patients with Grade 5 events (both respiratory failure; one in Study 0114, and one in Study 0314). The first event was described by the Investigator as "pulmonary disease due to disease progression," considered unrelated to tagraxofusp. The event of respiratory failure in the second patient was also considered unrelated to tagraxofusp. With the exception of 2 patients whose treatment was interrupted because of TEAEs considered related to tagraxofusp (Study 0114, [Grade 4 respiratory failure] and [Grade 3 angioedema; both BPDCN]), all other patients continued tagraxofusp despite the occurrence of a hypersensitivity event.

Overall, a hypersensitivity event was serious for 9 (6%) patients, including pneumonitis and respiratory failure (3 patients [2%] and 4 patients [3%], respectively) and single <1% cases of allergic transfusion reaction, angioedema, and rash.

Tumour Lysis Syndrome

All Patients in the Summary of Clinical Safety Pool

Overall, 11 (8%) patients experienced tumour lysis syndrome, including 5 (11%) of 47 BPDCN patients and 2 (4%) of 49 AML patients in Study 0114 and 4 (14%) of 29 patients in Study 0314, all of whom received tagraxofusp at 12 or 16 µg/kg/day. This event was considered by the Investigator to be tagraxofusp-related for 5 of these 11 patients. All but 1 case of tumour lysis syndrome were ≥Grade 3 in intensity and 3 cases were serious. Tumour lysis syndrome was Grade 5 in intensity for 1 AML patient (Study 0114, Patient 07-004; AML; 16 µg/kg/day), with this event considered by the Investigator to be secondary to disease progression and unrelated to tagraxofusp.

Among the 7 patients who experienced tumour lysis syndrome in Study 0114, 3 patients, including 1 each with AML, first-line BPDCN, and R/R BPDCN, had the event occur in the setting of progressive disease after starting at least 2 cycles of tagraxofusp. Tumour lysis syndrome was considered unrelated to tagraxofusp for all 3 of these patients. The remaining 4 patients experienced tumour lysis syndrome in C1, with the onset occurring after 1 or 2 doses of tagraxofusp in most patients, suggesting that tagraxofusp may cause rapid tumour lysis as a result of its anti-tumour activity.

Eye Disorders

All Patients in the Summary of Clinical Safety Pool

Overall, 18% (26/141) of patients experienced a TEAE within the MedDRA SOC "eye disorders." The only eye disorders that occurred for >2 patients overall were vision blurred (verbatim terms blurred vision, blurry vision, or fuzzy vision) (6% [8/141]) and conjunctival haemorrhage (4% [6/141]).

One BPDCN patient experienced a serious eye disorder, eye pain, which was considered secondary to facial skin lesions and unrelated to tagraxofusp.

Veno-Occlusive Disease

In Study 0114, patients may have undergone SCT after experiencing a tagraxofusp-induced remission or after receiving alternate therapy subsequent to discontinuing tagraxofusp. A total of 3 of 26 patients who underwent SCT at any time after tagraxofusp treatment in Study 0114 were reported to have experienced VOD post-SCT, with 2 of these patients receiving alternate therapy before SCT. The risk of VOD has been attributed to conditioning regimens and specific chemotherapeutics used in preparing a patient for SCT. Further, given that 2 of the 3 patients underwent intervening therapy before the diagnosis of VOD, it is unclear if tagraxofusp played a role in the event.

Choroid Plexitis

Repeat-dose toxicity studies with tagraxofusp in primates performed prior to enrollment in Investigator-sponsored Study 50047 revealed choroid plexitis as a potential drug-associated toxicity.

To monitor for this potential toxicity in the clinic, assessments for headaches and neurological signs and symptoms were required in Investigator-sponsored Study 50047 among the patients treated with Regimen A (dosing every other day for up to 6 doses). There were no clinical findings consistent with this toxicity. Consequently, this monitoring was removed from the protocol for Regimen B (daily dosing × 5) and was not employed in Stemline-sponsored studies. No findings consistent with this toxicity were seen among the 46 patients treated with Regimen B in Study 50047 or the 141 patients in the SCS pool.

Serious adverse event/deaths

A summary of SAEs reported for >1 patient in the SCS pool, by MedDRA SOC and PT is presented in Table 84, overall and by indication/study. The distribution of SAEs was generally consistent across disease types.

Table 84. Serious Treatment-Emergent Adverse Events Reported by >1 Patient: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study, by MedDRA SOC and Preferred Term (Safety Population)

MedDRA System Organ Class/ Preferred Term	Stemline-Sponsored Study				
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=16) n (%)	Study 0314 (N=29) n (%)	Total (N=141) n (%)
At Least 1 Treatment-Emergent SAE	23 (48.9)	33 (67.3)	8 (50.0)	17 (58.6)	81 (57.4)
Blood and lymphatic system disorders	2 (4.3)	9 (18.4)	1 (6.3)	1 (3.4)	13 (9.2)
Febrile neutropenia	1 (2.1)	8 (16.3)	1 (6.3)	0	10 (7.1)
Gastrointestinal disorders	0	2 (4.1)	2 (12.5)	2 (6.9)	6 (4.3)
Upper gastrointestinal haemorrhage	0	1 (2.0)	0	1 (3.4)	2 (1.4)
General disorders and administration site conditions	5 (10.6)	4 (8.2)	1 (6.3)	6 (20.7)	16 (11.3)
Disease progression	0	2 (4.1)	0	0	2 (1.4)
Fatigue	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Pyrexia	3 (6.4)	1 (2.0)	1 (6.3)	3 (10.3)	8 (5.7)
Infections and infestations	2 (4.3)	12 (24.5)	1 (6.3)	5 (17.2)	20 (14.2)
Lung infection	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Pneumonia	1 (2.1)	4 (8.2)	0	0	5 (3.5)
Sepsis	0	3 (6.1)	0	0	3 (2.1)
Injury, poisoning and procedural complications	1 (2.1)	3 (6.1)	0	0	4 (2.8)
Infusion-related reaction	1 (2.1)	1 (2.0)	0	0	2 (1.4)
Investigations	2 (4.3)	3 (6.1)	0	0	5 (3.5)
Aspartate aminotransferase increased	2 (4.3)	1 (2.0)	0	0	3 (2.1)
Metabolism and nutrition disorders	2 (4.3)	4 (8.2)	0	1 (3.4)	7 (5.0)
Tumour lysis syndrome	1 (2.1)	2 (4.1)	0	0	3 (2.1)
Nervous system disorders	2 (4.3)	3 (6.1)	0	4 (13.8)	9 (6.4)
Cerebrovascular accident	0	0	0	2 (6.9)	2 (1.4)
Renal and urinary disorders	0	1 (2.0)	0	2 (6.9)	3 (2.1)
Acute kidney injury	0	1 (2.0)	0	2 (6.9)	3 (2.1)
Respiratory, thoracic and mediastinal disorders	1 (2.1)	5 (10.2)	1 (6.3)	3 (10.3)	10 (7.1)
Pneumonitis	0	1 (2.0)	1 (6.3)	1 (3.4)	3 (2.1)
Pulmonary oedema	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Respiratory failure	1 (2.1)	2 (4.1)	0	1 (3.4)	4 (2.8)
Vascular disorders	7 (14.9)	9 (18.4)	2 (12.5)	3 (10.3)	21 (14.9)
Capillary leak syndrome	4 (8.5)	8 (16.3)	2 (12.5)	2 (6.9)	16 (11.3)
Hypertension	2 (4.3)	0	0	0	2 (1.4)
Hypotension	1 (2.1)	1 (2.0)	0	0	2 (1.4)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT. If a patient experienced more than one event within a given system organ class, that patient was counted only once for that system organ class.
Source: SCS Table 1.4.6.1.

For 36 (26%) of 141 patients in the SCS pool, at least 1 SAE was considered by the Investigator to be tagraxofusp-related. Tagraxofusp-related SAEs reported for >1 patient included CLS (16 patients; 11%); febrile neutropenia (4 patients; 3%); AST increased (3 patients; 2%); and IRR, pyrexia, and pulmonary oedema (each 2 patients; 2%).

Deaths among All Patients in the Summary of Clinical Safety Pool

A listing of patients with Grade 5 TEAEs, by study and indication, is presented in Table 85.

Table 85. Grade 5 TEAEs, by Indication/Study and Patient

Patient Number	Age/ Race/ Sex	Preferred Term/ System Organ Class/ AE Verbatim Term	Start Day[1]	Action Taken[2]	Relationship[3]
STUDY 0114					
First-line BPDCN					
[redacted]		Capillary leak syndrome/ Vascular disorders/ Capillary leak syndrome	4P	None	Related
		Capillary leak syndrome/ Vascular disorders/ Capillary leak syndrome	2P	None	Related
R/R BPDCN					
[redacted]		Respiratory failure/ Respiratory, thoracic and mediastinal disorders/ Respiratory failure (pulmonary disease due to disease progression)	8P	None	Not related
AML					
[redacted]		Haemorrhage intracranial/ Nervous system disorders/ Intracranial haemorrhage	23P	None	Not related
		Capillary leak syndrome/ Vascular disorders/ Capillary leak syndrome (CLS)	2P	None	Related
		Tumour lysis syndrome/ Metabolism and nutrition disorders/ Tumour lysis syndrome	1P	Inter	Not related
		Acute kidney injury/ Renal and urinary disorders/ Acute renal failure	3P	Discon	Not related
		Cardiac arrest/ Cardiac disorders/ Cardiac arrest	3P	None	Not related
		Disease progression/ General disorders and administration site conditions/ Progressive disease	7P	None	Not related
		Myocardial infarction/ Cardiac disorders/ Myocardial infarction	27P	None	Not related
		Pneumonia/ Infections and infestations/ Lung infection (pneumonia)	6P	Discon	Not related
		Disease progression/ General disorders and administration site conditions/ Disease progression	1P	Discon	Not related

Patient Number	Age/ Race/ Sex	Preferred Term/ System Organ Class/ AE Verbatim Term	Start Day[1]	Action Taken[2]	Relationship[3]
Study 0314					
[redacted]		Cardiopulmonary failure/ Cardiac disorders/ Terminal cardiorespiratory failure secondary to progressive myeloproliferation	24P	-	Not related
[redacted]		Abdominal wall haematoma/ Gastrointestinal disorders/ Rectus sheath haematoma	6P	Discon	Not related
		Acute kidney injury/ Renal and urinary disorders/ Acute kidney injury	6P	Discon	Not related
		Multiple organ dysfunction syndrome/ General disorders and administration site conditions/ Multi organ failure	6P	Discon	Not related
		Hyperkalaemia/ Metabolism and nutrition disorders/ hyperkalaemia	6P	Discon	Not related
		Urinary tract disorder/ Renal and urinary disorders/ renal other- compressive uropathy	6P	Discon	Not related
		Shock haemorrhagic/ Vascular disorders/ Haemorrhagic shock	6P	Discon	Not related
[redacted]		Cerebrovascular accident/ Nervous system disorders/ Stroke	5P	Discon	Related
[redacted]		Lung infection/ Infections and infestations/ Lung infection	10P	None	Not related
[redacted]		Respiratory failure/ Respiratory, thoracic and mediastinal disorders/ Respiratory failure	27P	-	Not related
		Cerebral infarction/ Nervous system disorders/ Intracranial infarct	27P	-	Not related

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; Black = black or African American; Discon = discontinued; F = female; M= male.

1 Relative day to first dose if event occurs on treatment (ex: '5') with last day designated as 'L' (ex: '5L'). Relative day to last dose if event occurs post treatment designated as 'P' (ex: '5P').

2 None = Dose not changed. Discon = Drug withdrawn. Inter = Drug interrupted. Reduce = Dose reduced.

3 Relationship presented was according to the Investigator's assessment. The narrative summary provides the Sponsor's assessment of relationship in addition to that of the Investigator.

Source: SCS Table 1.4.6.1 and Study 0114, Table 14.3.2.1.

Laboratory findings

Haematology

Patients with BPDCN in Study 0114

A summary of the proportion of patients who entered the study with normal values or Grade 1 or 2 abnormalities for haemoglobin, platelet count, and ANC and who had shifts on study to a Grade 3 or 4 abnormality is provided in Table 86.

Table 86. Proportion of BPDCN Patients Treated with Tagraxofusp with Normal (Grade 0) or Grade 1 or 2 Haematology Values at Baseline Who Shifted to Grade 3 or 4 Abnormalities as Worst Value on Study (Safety Population)

Parameter (Units)/ Time point	All BPDCN Patients (N=47) n/N[1] (%)
Haemoglobin (g/L)	
Shift to Grade 3 (low)	8 (17.0)
Shift to Grade 4 (low)	0
Platelet Count (10^9/L)	
Shift to Grade 3 (low)	11 (23.4)
Shift to Grade 4 (low)	9 (19.1)
ANC (10^9/L)	
Shift to Grade 3 (low)	8 (17.0)
Shift to Grade 4 (low)	5 (10.6)

Abbreviations: ANC = absolute neutrophil count; BPDCN = blastic plasmacytoid dendritic cell neoplasm.
1 N was based on the number of patients with both Baseline and post-treatment values.
Source: SCS, Table 1.5.3.1A.

All Patients in the Summary of Clinical Safety Pool

According to the applicant, evaluation of haematology results among all patients in the SCS pool (as of the data cutoff of 25 Sep 2017) yielded findings similar to those seen in BPDCN patients, with no meaningful changes over time during treatment with tagraxofusp.

Liver Function Tests

Patients with BPDCN in Study 0114

Baseline median ALT and AST were both 22.0 U/L among all BPDCN patients in Study 0114. With regard to ALT, progressively greater median increases from baseline in ALT were seen over the dosing period in C1 among all BPDCN patients. Thereafter, a return toward baseline in median ALT was seen by C2Inf1. A similar, but notably less pronounced pattern was seen in C2.

Kaplan-Meier analysis of time to first onset of elevated ALT was performed for BPDCN patients treated with tagraxofusp at 12 µg/kg/day. The median time to first onset of ALT >3×ULN was short, irrespective of line of therapy, occurring 0.8 and 0.3 months after treatment initiation in first-line and R/R BPDCN patients, respectively.

Progressively greater median increases from baseline also were seen in AST over the dosing period in C1 among BPDCN patients, with a maximum median increase of 90.0 U/L seen on C1D8. Thereafter, a return to baseline in median AST was seen by C2Inf1. With regard to AST, 40% (19/47) and 2% (1/47) of BPDCN patients with normal AST or Grade 1 or 2 AST at baseline experienced a shift to Grade 3 or to Grade 4 elevated AST, respectively.

Two first-line BPDCN patients in this study met the laboratory criteria for Hy's Law, 1 based on the ALT and bilirubin criteria, and 1 based on AST and bilirubin criteria. The first patient's ALT level decreased to 57 U/L by C2D21, and then returned to normal range by C2Inf1 (actual value 24 U/L). AST at that time was 21 U/L. Similarly, the bilirubin level decreased to normal range (8.6 µmol/L) at the same time. No subsequent ALT elevations were reported for this patient. The patient's ALP values remained within normal range at all-time points assessed. No associated clinical events were reported. This patient discontinued tagraxofusp due to progressive disease 1 day after C7Inf1. The second patient died as a result of CLS 2 weeks after C1Inf5; the event of CLS was considered tagraxofusp-related.

All Patients in the Summary of Clinical Safety Pool

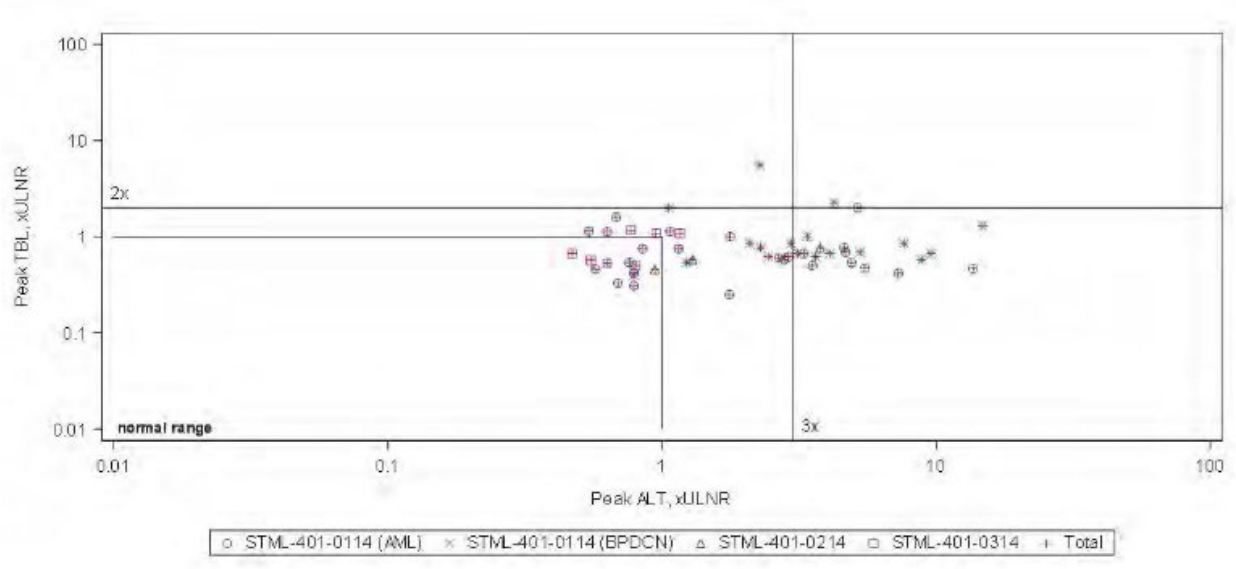
An overall summary of treatment-emergent LFT values >ULN among all patients in the SCS pool is presented overall and by indication/study in Table 87.

Table 87. Liver Function Tests with Treatment-Emergent Values >ULN: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study (Safety Population)

Parameter	Stemline-Sponsored Study				Total (N=125)[1]
	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=14) n (%)	Study 0314 (N=15) n (%)	
AST (x ULN)					
>3 to ≤5	22 (46.8)	16 (32.7)	4 (28.6)	0	42 (33.6)
>5 to ≤10	17 (36.2)	11 (22.4)	2 (14.3)	1 (6.7)	31 (24.8)
>10 to ≤20	7 (14.9)	4 (8.2)	0	0	11 (8.8)
>20	1 (2.1)	4 (8.2)	0	0	5 (4.0)
ALT (x ULN)					
>3 to ≤5	23 (48.9)	18 (36.7)	3 (21.4)	0	44 (35.2)
>5 to ≤10	14 (29.8)	9 (18.4)	3 (21.4)	1 (6.7)	27 (21.6)
>10 to ≤20	4 (8.5)	3 (6.1)	1 (7.1)	0	8 (6.4)
>20	0	1 (2.0)	0	0	1 (0.8)
ALP (x ULN)					
>1.5	10 (21.3)	5 (10.2)	2 (14.3)	4 (26.7)	21 (16.8)
TBL (x ULN)					
>1.5 to ≤2	4 (8.5)	4 (8.2)	0	1 (6.7)	9 (7.2)
>2	4 (8.5)	1 (2.0)	0	1 (6.7)	6 (4.8)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AML = acute myeloid leukaemia; AST = aspartate aminotransferase; BPDCN = blastic plasmacytoid dendritic cell neoplasm; TBL = total bilirubin level; ULN = upper limit of normal.
1 Based on data cutoff of 25 Sep 2017.
Source: SCS, Table 1.6.1.1.

To assess for possible DILI, a figure plotting peak ALT versus peak total bilirubin within ±7 days (both on a logarithmic scale × ULN) was produced (see Figure 14); a similar analysis was performed for AST (Figure 15).



Abbreviations: ALT = alanine aminotransferase; AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; TBL = total bilirubin level; ULNR = upper limit of normal range.
Note: Data are based on data cutoff of 25 Sep 2017.

Figure 13. Hy's Law Candidates, Based on Peak ALT versus Peak Bilirubin: Patients in the Summary of Clinical Safety Pool (Safety Population)

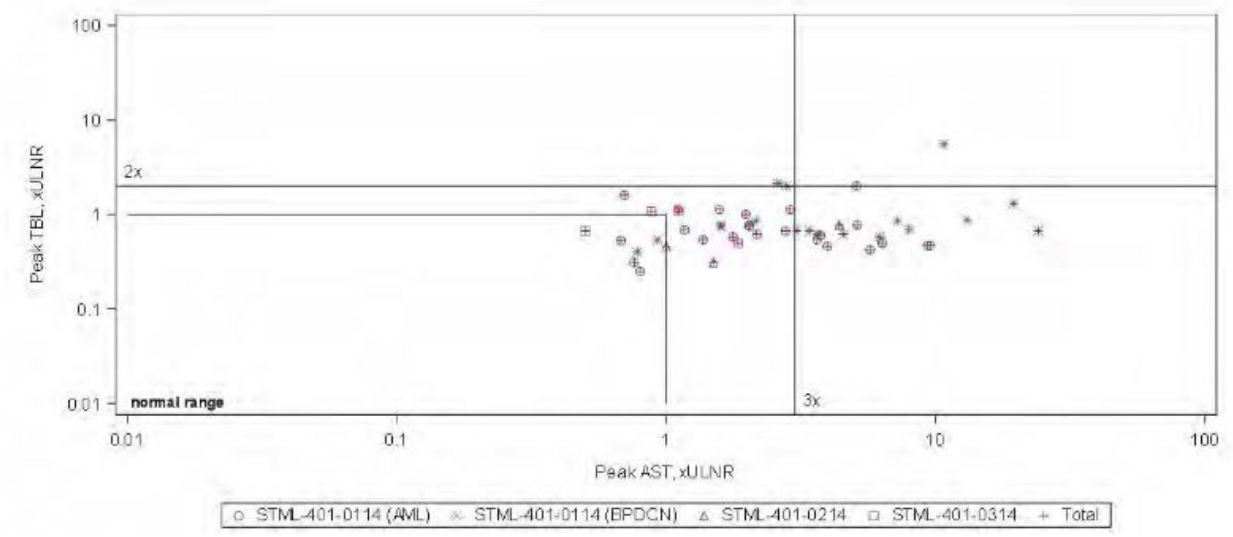


Figure 14. Hy's Law Candidates, Based on Peak AST versus Peak Bilirubin: Patients in the Summary of Clinical Safety Pool (Safety Population)

Albumin

The impact of tagraxofusp on changes in albumin levels during treatment are difficult to evaluate, given guidance within the protocols to actively manage and supplement albumin since hypoalbuminaemia may be a harbinger of impending or a symptom of active CLS.

Patients with BPDCN in Study 0114

Among BPDCN patients in C1, during which albumin supplementation was common (64% [30/47]), relatively small median decreases in albumin levels were seen over the infusion period. Over subsequent cycles, small median changes in albumin also were seen, with no median decreases seen at any time point through the end of C6.

All Patients in the Summary of Clinical Safety Pool

Among all 125 patients included in the analysis through the 25 Sep 2017 cut-off, in C1, during which albumin supplementation was common (42% [52/125]), relatively small median decreases in albumin were seen over the infusion period; thereafter, no median decrease from baseline in albumin was seen at any time point through the end of C6. Furthermore, no patient experienced a treatment-emergent shift to Grade 3 or 4 hypoalbuminaemia during the study.

Electrocardiogram Findings

Patients with BPDCN in Study 0114

Neither acute nor chronic treatment with tagraxofusp was associated with consistent changes in any of the ECG variables of HR, PR, QRS, or QTcF. On ECGs recorded pre-dose on tagraxofusp infusion days, most changes from baseline were small and negative. The 90% upper confidence limit for ΔQTcF was below the threshold of regulatory concern on all 34 post-baseline occasions in BPDCN patients. No patient experienced Torsades de pointes (Study 0114).

Five (11%) BPDCN patients had electrocardiogram QT prolonged reported as a TEAE. None of these patients experienced syncope or pre-syncope; only 1 had associated cardiac TEAEs (1 patient had 2 AEs of sinus tachycardia). No cases were considered serious or led to treatment discontinuation. Overall, 2 (4%) BPDCN patients had a clinically significant abnormal ECG finding at any time on study, including 1

first-line patient with ECG evidence of sinus tachycardia pre-infusion at C1Inf5 and 1 R/R BPDCN patient with ECG evidence of sinus tachycardia at C1Inf2.

Overall, 34% (16/47) of BPDCN patients had a cardiac disorder reported as a TEAE, with most individual cardiac disorders reported in 1 or 2 patients only. The only cardiac disorders reported for >2 patients were tachycardia (7 patients; 15%) and sinus tachycardia (3 patients; 6%).

All Patients in the Summary of Clinical Safety Pool

A summary of maximum changes from baseline in QTcF and QTcB is presented overall and by indication/study in Table 88 and by tagraxofusp dose in Table 89.

Table 88. Electrocardiogram Categorical Summary of QTcF and QTcB Intervals at Any Time on Study: All Patients in the Summary of Clinical Safety Pool, Overall and by Indication/Study (Safety Population)

		Indication / Study				
Parameter	Result	Study 0114 (BPDCN) (N=47) n (%)	Study 0114 (AML) (N=49) n (%)	Study 0214 (N=14) n (%)	Study 0314 (N=15) n (%)	Total (N=125)[1] n (%)
QTcF	>450 msec	12 (26.1)	14 (28.6)	7 (50.0)	5 (33.3)	38 (30.6)
	>480 msec	4 (8.7)	2 (4.1)	2 (14.3)	2 (13.3)	10 (8.1)
	>500 msec	3 (6.5)	0	0	2 (13.3)	5 (4.0)
	Increase >30 msec	11 (23.9)	8 (16.3)	1 (7.1)	4 (26.7)	24 (19.4)
	Increase >60 msec	2 (4.3)	0	0	2 (13.3)	4 (3.2)
QTcB	>450 msec	32 (69.6)	31 (63.3)	10 (71.4)	13 (86.7)	86 (69.4)
	>480 msec	6 (13.0)	12 (24.5)	6 (42.9)	3 (20.0)	27 (21.8)
	>500 msec	5 (10.9)	5 (10.2)	0	2 (13.3)	12 (9.7)
	Increase >30 msec	21 (45.7)	12 (24.5)	3 (21.4)	5 (33.3)	41 (33.1)
	Increase >60 msec	3 (6.5)	1 (2.0)	0	2 (13.3)	6 (4.8)

Abbreviations: AML = acute myeloid leukaemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; ECG = electrocardiogram; QTcB = QT Interval, Bazett; QTcF = QT Interval, Fridericia.
Note: Based on mean 12-lead triplicate ECG values. Patients were categorised by their mean QTcF or QTcB value at any point on study post-baseline. Increases were compared to baseline values.
1 Based on data cutoff of 25 Sep 2017.
Source: SCS, Table 1.8.2.1.

Table 89. Electrocardiogram Categorical Summary of QTcF and QTcB Intervals at Any Time on Study: All Patients in the Dose Level Pool, by Dose (Safety Population)

		Dose			
Parameter	Result	7 µg/kg/day (N=12) n (%)	9 µg/kg/day (N=9) n (%)	12 µg/kg/day (N=97) n (%)	Total (N=118)[1] n (%)
QTcF	>450 msec	4 (33.3)	3 (33.3)	28 (29.2)	35 (29.9)
	>480 msec	2 (16.7)	1 (11.1)	7 (7.3)	10 (8.5)
	>500 msec	1 (8.3)	0	4 (4.2)	5 (4.3)
	Increase >30 msec	1 (8.3)	1 (11.1)	21 (21.9)	23 (19.7)
	Increase >60 msec	0	0	4 (4.2)	4 (3.4)
QTcB	>450 msec	9 (75.0)	6 (66.7)	64 (66.7)	79 (67.5)
	>480 msec	3 925.0)	1 (11.1)	21 (21.9)	25 (21.4)
	>500 msec	1 98.3)	1 (11.1)	9 (9.4)	11 (9.4)
	Increase >30 msec	2 (16.7)	1 (11.1)	37 (38.5)	40 (34.2)
	Increase >60 msec	0	1 (11.1)	5 (5.2)	6 (5.1)

Abbreviations: ECG = Electrocardiogram; QTcB = QT Interval, Bazett; QTcF = QT Interval, Fridericia.
Note: Based on mean 12-lead triplicate ECG values. Patients were categorised by their mean QTcF or QTcB value at any point on study post-baseline. Increases were compared to baseline values.
1 Based on data cutoff of 25 Sep 2017.

In total, 6 (4%) of the 141 patients had electrocardiogram QT prolonged reported as a TEAE, all of whom received tagraxofusp 12 µg/kg/day. For 2 patients, this event was assessed as Grade 3 in intensity and as Grade 1 or 2 in intensity for the remaining 4 patients. Overall, 51 (36%) of 141 patients had a cardiac disorder reported as a TEAE. Cardiac disorders reported for >2 patients overall were tachycardia (24 patients; 17%), sinus tachycardia (13 patients; 9%), atrial fibrillation (4 patients; 3%), and bradycardia,

palpitations, pericardial effusion, and sinus bradycardia (each 3 patients; 2%). Fourteen (10%) patients experienced a tagraxofusp-related cardiac disorder, most commonly tachycardia (8 patients; 6%) and sinus tachycardia (4 patients; 3%). A serious cardiac disorder was considered tagraxofusp-related for 2 patients, including 1 case each of ventricular fibrillation (Study 0114) and pericardial effusion (Study 0314). Treatment was discontinued because of the event of pericardial effusion.

QTc/Exposure Analysis

Please refer to section on Clinical Pharmacology.

Safety in special populations

The applicant presented a summary of commonly occurring TEAEs and CLS by age, sex, weight and ECOG PS score (Table 90).

Table 90. Summary of commonly occurring TEAEs and CLS by age, sex, weight and ECOG PS score

	Age			Sex		Weight		Baseline ECOG PS Score	
TEAE	<65 years (N=63) n (%)	≥65 years (N=78) n (%)	≥75 years[1] (N=30) n (%)	Male (N=95) n (%)	Female (N=46) n (%)	46.7 to 85.2 kg (N=75) n (%)	85.5 to 122.6 kg (N=48) n (%)	0 (N=42) n (%)	1-2 (N=83) n (%)
Alanine aminotransferase increased	33 (55.6)	42 (53.8)	17 (56.7)	53 (55.8)	24 (52.2)	39 (51.3)	29 (60.4)	28 (66.7)	42 (50.6)
Aspartate aminotransferase increased	35 (55.6)	37 (47.4)	16 (53.3)	51 (53.7)	21 (45.7)	39 (51.3)	28 (58.3)	27 (64.3)	42 (50.6)
Hypoalbuminaemia	29 (46.0)	48 (61.5)	20 (66.7)	53 (55.8)	24 (52.2)	39 (51.3)	26 (54.2)	25 (59.5)	42 (50.6)
Fatigue	34 (54.0)	36 (46.2)	13 (43.3)	40 (42.1)	30 (65.2)	38 (50.0)	22 (45.8)	27 (64.3)	34 (41.0)
Nausea	32 (50.8)	37 (47.4)	13 (43.3)	40 (42.1)	29 (63.0)	31 (40.8)	26 (54.2)	21 (50.0)	37 (44.6)
Oedema peripheral	22 (34.9)	40 (51.3)	18 (60.0)	43 (45.3)	19 (41.3)	35 (46.1)	20 (41.7)	19 (45.2)	37 (44.6)
Pyrexia	35 (55.6)	26 (33.3)	9 (30.0)	40 (42.1)	21 (45.7)	30 (39.5)	25 (52.1)	18 (42.9)	37 (44.6)
Thrombocytopenia	23 (36.5)	30 (38.5)	14 (46.7)	35 (36.8)	18 (39.1)	27 (35.5)	18 (37.5)	21 (50.0)	25 (30.1)
Headache	20 (31.7)	22 (28.2)	6 (20.0)	23 (24.2)	19 (41.3)	22 (28.9)	16 (33.3)	15 (35.7)	24 (28.9)
Hyperglycaemia	18 (28.6)	22 (28.2)	10 (33.3)	26 (27.4)	14 (30.4)	24 (31.6)	14 (29.2)	16 (38.1)	22 (26.5)
Capillary leak syndrome	13 (20.6)	13 (16.7)	7 (23.3)	19 (20.0)	7 (15.2)	13 (17.1)	11 (22.9)	9 (21.4)	16 (19.3)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Score; MedDRA=Medical Dictionary for Regulatory Activities: PT = preferred term; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 19.0. If a patient experienced more than one event with a given PT, that patient was counted only once for that PT. For weight measurements, Tertile 1 = 46.7 to 85.2 kg, Tertile 2 = 85.5 to 122.6 kg, and Tertile 3 = 128.2 to 162.4 kg.
1 Patients aged ≥75 years are included in both the ≥65 years subgroup and ≥75 years subgroup.
Source: SCS, Table 1.4.2.1.1, Table 1.4.2.1.3, Table 1.4.2.1.7, and Table 1.4.2.1.8.

Immunological events

In study 0114

Immune response to SL-401 was assessed using two immunoassays. The first assay detected reactivity directed against SL-401 (ADA) and the second assay detected reactivity against the IL-3 portion of SL-401 (AIA).

Results - ADA

The baseline summary and characterisation of ADAs for all patients is shown in Table 91 by disease and overall. All 96 patients enrolled had baseline samples tested for ADA with a reportable ADA result.

Table 91. Summary and Characterisation of Baseline Antidrug Antibodies in Study 0114 Patients by Disease and Overall

	First-Line BPDCN (N=32)	R/R BPDCN (N=15)	AML (N=49)	All Patients (N=96)
Baseline Summary (All Patients), N	**32**	**15**	**49**	**96**
ADA-negative, n (%)	3 (9)	2 (13)	0	5 (5)
ADA-positive, n (%)	29 (91)	13 (87)	49 (100)	91 (95)
Baseline titer (median, IQR and maximum)	800 (80, 8000) 80,000	800 (80, 800) 8000	800 (800, 800) 80,000	800 (800, 800) 80,000
Baseline ADA-positive and NAb-positive, n/N (%)	7/29 (24)	3/13 (23)	9/49 (18)	19/91 (21)
Baseline Summary (Evaluable Population), N	**31**	**14**	**40**	**85**
ADA-negative, n (%)	3 (10)	1 (7)	0	4 (5)
ADA-positive, n (%)	28 (90)	13 (93)	40 (100)	81 (95)
Baseline ADA-positive and NAb-positive, n/N (%)	6/28 (21)	3/13 (23)	8/40 (20)	17/81 (21)

Abbreviations: ADA = antidrug antibody; AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; IQR = interquartile range; NAb = neutralizing antibody; R/R = relapsed/refractory.
Note: The Immunogenicity Population (All Patients) included all patients with a baseline assessment. The Evaluable Immunogenicity Population (Evaluable Population) included patients having a baseline assessment and at least 1 postbaseline assessment.
Source: Table 14.3.5.15.1, Table 14.3.5.15A, Table 14.3.5.15C, and Table 14.3.5.16.1.

Of the 81 ADA evaluable patients who were ADA-positive at baseline, 57 (70%) had a significant increase (≥100-fold) in ADA titer (treatment-boosted ADA) after drug administration (Table 92).

Table 92. Treatment-boosted and Treatment-induced Antidrug Antibody Incidence, by Disease and Overall (Evaluable Immunogenicity Population)

	First-Line BPDCN (N=31)	R/R BPDCN (N=14)	AML (N=40)	All Patients (N=85)
Treatment-boosted ADA Incidence				
Baseline ADA-positive, N	28	13	40	81
Treatment-boosted ADA (≥ 100-fold titer increase), n (%)	27 (96)	11 (85)	19 (48)	57 (70)
Peak positive titer (IQR)	80,000,000 (800,000, 800,000)	80,000,000 (800, 440,000)	80,000,000 (80,000, 800,000)	80,000,000 (800, 800,000)
Maximum fold increase in titer[a]	100,000	1,000,000	100,000	1,000,000
Timing of maximum fold increase in titer	Cycle 2/Day 15	Cycle 1/Day 15	Cycle 2/Day 15	Cycle 2/Day 15
Treatment-induced ADA Incidence				
Baseline ADA-negative, N	3	1	0	4
Treatment-induced ADA, n (%)	3 (100)	1 (100)	0	4 (100)
Peak positive titer (IQR)	80,000 (80,000, 80,000)	80,000 (80,000, 80,000)	N/A	80,000 (80,000, 80,000)
Timing of peak positive titer	Cycle 2/Day 15	Cycle 2/Day 15	N/A	Cycle 2/Day 15
Overall ADA and NAb Incidence After Treatment				
Treatment-boosted + treatment-induced ADA-positive, n/N (%)	30/31 (97)	12/14 (86)	19/40 (48)	61/85 (72)
Total ADA-positive after treatment, n/N (%)	31/31 (100)	14/14 (100)	40/40 (100)	85/85 (100)
Total NAb-positive after treatment, n/N (%)	27/28 (96)	12/13 (92)	30/40 (75)	69/81 (85)

Abbreviations: ADA = antidrug antibody; AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; IQR = interquartile range; N/A = not applicable; NAb = neutralizing antibody; R/R = relapsed/refractory.
[a] Maximum fold increase in titer = ratio of peak titer after administration to baseline median titer.
Source: Table 14.3.5.15.2, Table 14.3.5.16A, Table 14.3.5.17A, and Table 14.3.5.18A.

According to the applicant, after SL-401 treatment, 100% (85 of 85 ADA-evaluable patients) were ADA-positive and 85% (69 of 81 NAb-evaluable patients) were NAb-positive. The ADA titer remained stable over the study course with no differences between indications (Figure 16).

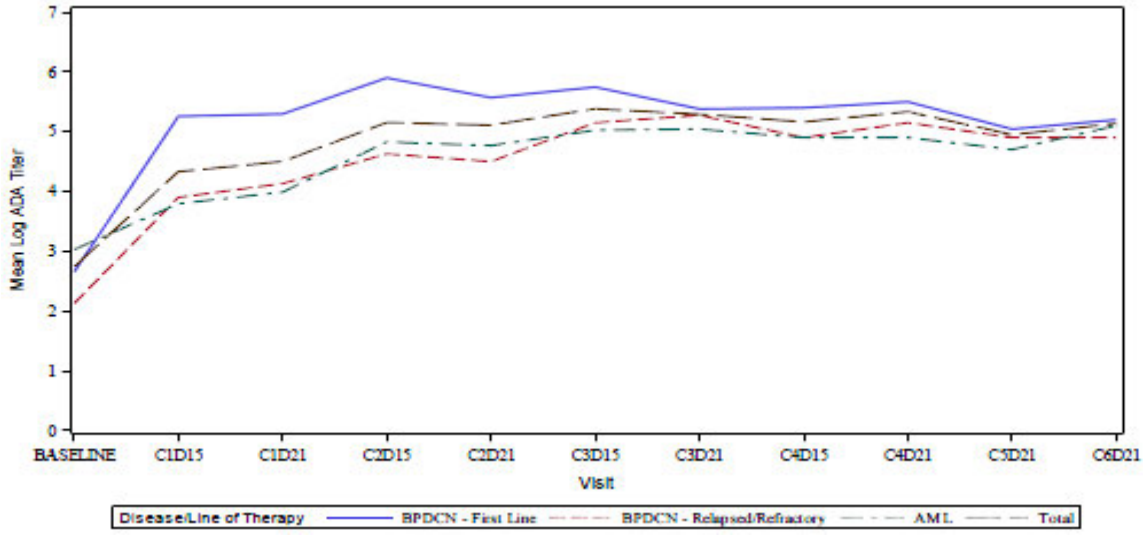


Figure 15. Mean Logarithmic Antidrug Antibody Titer, by Visit and Indication (Evaluable Immunogenicity Population)

Results - AIA

The baseline summary and characterization of AIA for all patients and the immunogenicity evaluable population are shown in Table 93 by disease and overall. All 96 patients enrolled had baseline samples tested for AIA with a reportable result.

Table 93. Summary and Characterization of Baseline Anti-human Interleukin-3 Antibody Status, by Disease and Overall

	First-Line BPDCN (N=32)	R/R BPDCN (N=15)	AML (N=49)	All Patients (N=96)
Baseline Summary (All Patients), N	**32**	**15**	**49**	**96**
AIA-negative, n (%)	32 (100)	14 (93)	49 (100)	95 (99)
AIA-positive, n (%)	0	1 (7)[a]	0	1 (1)[a]
Baseline Summary (Evaluable Population), N	**31**	**14**	**40**	**85**
AIA-negative, n (%)	31 (100)	13 (93)	40 (100)	84 (99)
AIA-positive, n (%)	0	1 (7)[a]	0	1 (1)[a]

Abbreviations: AIA = anti-human interleukin-3 antibody; AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; FL = first-line; IQR = interquartile range; NA = not applicable; R/R = relapsed/refractory.

[a] Titer of 1 patient with positive AIA antibody at baseline was 25.

Source: Table 14.3.5.15.1 and Table 14.3.5.15.2.

As shown in Table 94, of the 84 evaluable patients who were negative for AIA at baseline, 57 (68%) converted to AIA-positive after treatment (treatment-induced).

Table 94. Treatment-boosted and Treatment-induced Anti-human Interleukin-3 Antibody Incidence, by Disease and Overall (Evaluable Immunogenicity Population)

	First-Line BPDCN (N=32)	R/R BPDCN (N=15)	AML (N=49)	All Patients (N=96)
Evaluable Population, N	**31**	**14**	**40**	**85**
Treatment-boosted AIA Incidence				
Baseline AIA-positive, N	0	1	0	1
Treatment-boosted AIA (≥ 4-fold titer increase), n (%)	0	1 (100)[a]	0	1 (100)[a]
Peak positive titer (IQR)	N/A	3200 (3200, 3200)	N/A	3200 (3200, 3200)
Maximum fold increase in titer[b]	N/A	128	N/A	128
Timing of maximum fold increase in titer	N/A	Cycle 3/Day 15	N/A	Cycle 3/Day 15
Treatment-induced AIA Incidence				
Baseline AIA-negative, N	31	13	40	84
Treatment-induced AIA, n (%)	28 (90)	12 (92)	16 (40)	56 (67)
Peak positive titer (IQR)	51,200 (1600, 12,800)	51,200 (1600, 51,200)	819,200 (1, 25,600)	819,200 (1, 6400)
Maximum fold increase in titer[b]	51,200	51,200	819,200	819,200
Timing of maximum fold increase in titer	Cycle 3/Day 15	Cycle 3/Day 15	Cycle 2/Day 21	Cycle 2/Day 21
Overall AIA Incidence After Treatment				
Treatment-boosted + treatment-induced AIA-positive, n/N (%)	28/31 (90)	13/14 (93)	16/40 (40)	57/85 (67)
Total AIA-positive after treatment, n/N (%)	29/31 (94)	13/14 (93)	16/40 (40)	58/85 (68)
Total AIA NAb-positive after treatment, n/N (%)	27/28 (96)	10/13 (77)	9/16 (56)	46/57 (81)

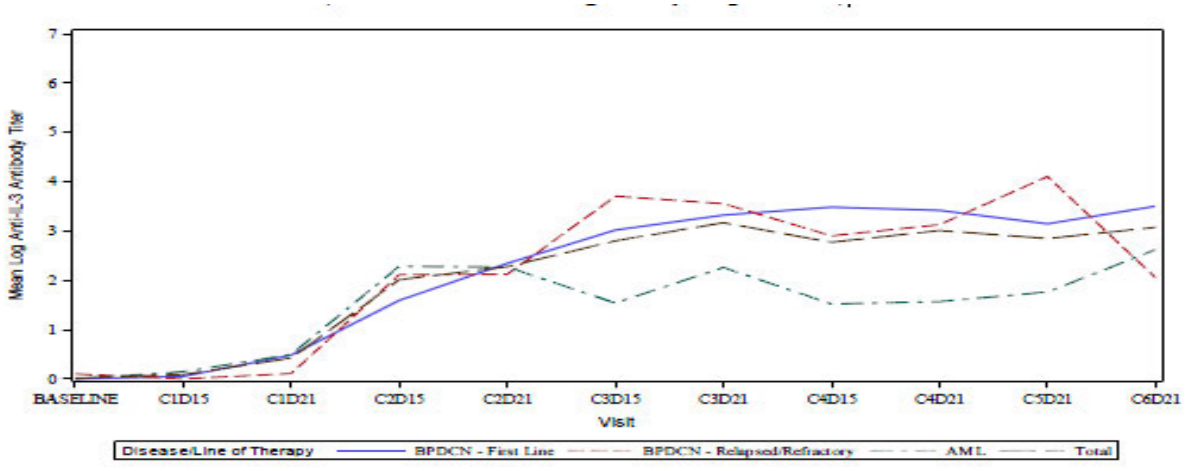
Abbreviations: AIA = anti-human interleukin-3 antibody; AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; FL = first-line; IQR = interquartile range; NA = not applicable; NAb = neutralizing antibody; R/R = relapsed/refractory.

[a] Titer of 1 patient with positive AIA antibody at baseline was 25.

[b] Fold increase in titer = ratio of peak titer after administration to baseline titer.

Source: Table 14.3.5.15.1, Table 14.3.5.15.2, Table 14.3.5.15B, Table 14.3.5.15D, Table 14.3.5.16B, Table 14.3.5.17B, and Table 14.3.5.18B.

The AIA titers increased through C3D15 and then generally remained stable over the study course for patients with BPDCN and overall but showed some fluctuation for patients with AML (Figure 17).



Abbreviations: AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CxDx = Cycle x, Day x; IL-3 = interleukin-3; Log = Log_{10}.

Source: Table 14.3.5.16B.

Figure 16. Mean Logarithmic Anti-human Interleukin-3 Antibody Titer, by Visit and Indication (Evaluable Immunogenicity Population)

Pooled data across all 4 tagraxofusp clinical studies

The characteristics of immune response to tagraxofusp were expected given the high childhood and booster diphtheria vaccination rate in the population:

• The majority of patients with baseline samples available (96%; 140/146), regardless of disease diagnosis, were positive for ADAs at baseline; 23% of patients were ADA NAb-positive at baseline.

• Of the 131 evaluable patients (i.e. patients with baseline and post-baseline samples available), 126 (96%) had ADA reactive antibodies at baseline and 29 (23%) were also NAb positive.

• By the end of treatment, all 131 evaluable patients (100%) were ADA-positive and 116 (89%) of the 130 tested were NAb-positive.

• The ADA titre increased by C1D15 and remained stable over the study course with minor differences between dose groups. The peak increase in titre (1000-fold) was reached by C2D15. The maximum titre of 80,000,000 was observed in more than one patient and in multiple cycles.

In contrast, 99% (144/146) of patients with samples available were negative for AIA at baseline.

The hIL-3 immune response was characterised as follows:

• Of the 132 evaluable patients, 130 (98%) were AIA-negative at baseline and 2 (2%) were AIA-positive; both AIA-positive patients were NAb negative at baseline.

• After treatment, 97 (73%) of the 132 evaluable patients were AIA-positive and 74 (76%) of the 97 were NAb-positive.

• The AIA titre median titre started to increase Cycle 2 with peak median titres at C4D15.

Analysis of Clinical Impact Analyses (Post-hoc)

The potential impact of ADA on clinical measurements, including exposure (duration of treatment, number of cycles and doses), efficacy (CR+CRc rate, duration of CR/CRc, time to CR/CRc), AESIs (hypoalbuminemia, CLS, and

Table 95. Antidrug Antibodies and Clinical Measurements Used in the Analyses

Assessment Type	Measurements
ADA measurements	• Tagraxofusp NAb at baseline and after treatment (ADA NAb) • AIA after treatment • AIA NAb after treatment
Duration of exposure assessments	• Duration of exposure in days • Number of cycles started • Number of doses received
Pharmacokinetic measurements	• AUC_{last} on Cycle 1 Infusion 1 • AUC_{last} on Cycle 3 Infusion 1 • Clearance on Cycle 1 Infusion 1
Efficacy measurements	• CR+CRc rate • Duration of CR/CRc in months • Time to CR/CRc in days
Safety measurements	• TEAEs at any Grade • AESIs (hypoalbuminemia, capillary leak syndrome, elevated transaminases)

Abbreviations: ADA = antidrug antibody; AESI = adverse event of special interest; AIA = anti-human interleukin-3 antibody; AUC_{last} = area under the concentration-time curve from time 0 to time of last measurable concentration; CR = complete response; CRc = complete response with minimal residual skin abnormality; NAb = neutralizing antibody; TEAE = treatment-emergent adverse event.

Comparisons that resulted in P values that were statistically significant at the 0.05 level are presented in Table 96.

Table 96. Statistical Comparisons Resulting in P Values <0.05

Table Source	Line of Therapy	Comparison (Sample Size)	Parameter	Result (95% CI for the Difference Between Subgroups)	*P* Value
14.3.5.35A	FL BPDCN	Baseline ADA NAb+ (n=7) vs Baseline ADA NAb- (n=22)	Median AUC_{last} C1I1 (h·µg/L)	7.16 vs 88.30 (-154.84, -2.60)	0.0277
		Baseline ADA NAb+ (n=7) vs Baseline ADA NAb- (n=22)	Median AUC_{last} C3I1 (h·µg/L)	0.43 vs 0.00 (NE, NE)	0.0481

Abbreviations: ADA = antidrug antibody; AUC_{last} = area under the concentration-time curve from time 0 to time of last measurable concentration; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CxIx = Cycle x Infusion x; FL = first-line; NAb = neutralising antibody; NE = non-estimable.

Across the 83 statistical tests performed, only 2 comparisons resulted in P values <0.05, both related to AUClast. Median AUClast in C1D1 was significantly lower in the 7 patients who were ADA NAb-positive than in the 22 patients who were ADA NAb-negative at baseline. At C3D1, the difference in AUClast between patients who were ADA Nab-positive and patients who were ADA Nab-negative at baseline, although statistically significant, was small with a non-estimable 95% CI for the between-group difference. Other ADA measurements did not impact levels of measurable drug.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with Tagraxofusp.

Discontinuation due to AEs

Adverse Events Leading to Tagraxofusp Discontinuation among All Patients in the Summary of Clinical Safety Pool

Table 97. Adverse Events Leading to Tagraxofusp Discontinuation

Table 1.4.13.1

Treatment-Emergent Adverse Events Resulting in SL-401 Withdrawal/Discontinuation by MedDRA System Organ Class and Preferred Term: All Patients in Monotherapy Studies (Safety Population)

MedDRA SOC Preferred Term	STML-401-0114 (BPDCN) (N=47) n(%)	STML-401-0114 (AML) (N=49) n(%)	STML-401-0214 (N=16) n(%)	STML-401-0314 (N=29) n(%)	Total (N=141) n(%)
At Least 1 TEAE Resulting in SL-401 Withdrawn	1 (2.1)	8 (16.3)	2 (12.5)	4 (13.8)	15 (10.6)
Blood and lymphatic system disorders	0	0	0	1 (3.4)	1 (0.7)
Leukocytosis	0	0	0	1 (3.4)	1 (0.7)
Cardiac disorders	0	0	0	1 (3.4)	1 (0.7)
Pericardial effusion	0	0	0	1 (3.4)	1 (0.7)
Gastrointestinal disorders	0	0	0	1 (3.4)	1 (0.7)
Abdominal wall haematoma	0	0	0	1 (3.4)	1 (0.7)
General disorders and administration site conditions	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Disease progression	0	1 (2.0)	0	0	1 (0.7)
Multiple organ dysfunction syndrome	0	0	0	1 (3.4)	1 (0.7)
Hepatobiliary disorders	0	1 (2.0)	0	0	1 (0.7)
Hepatic failure	0	1 (2.0)	0	0	1 (0.7)
Infections and infestations	0	2 (4.1)	1 (6.3)	0	3 (2.1)
Pneumonia	0	1 (2.0)	0	0	1 (0.7)
Septic shock	0	1 (2.0)	0	0	1 (0.7)
Staphylococcal bacteraemia	0	0	1 (6.3)	0	1 (0.7)
Injury, poisoning and procedural complications	0	1 (2.0)	0	0	1 (0.7)
Infusion related reaction	0	1 (2.0)	0	0	1 (0.7)

Note: BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm. AML = Acute Myeloid Leukemia. TEAE = Treatment-Emergent Adverse Event. Adverse events are coded using MedDRA version 19.0. If a patient experienced more than one event with a given preferred term, that patient is counted only once for that preferred term. If a patient experienced more than one event with a given system organ class, that patient is counted only once for that system organ class.
Source STML-401-0214 and 0314: Listings 16.2.7.1, 16.2.7.2; STML-401-0114 CSR Listings 16.2.7.1, 16.2.7.2

Table 1.4.13.1

Treatment-Emergent Adverse Events Resulting in SL-401 Withdrawal/Discontinuation by MedDRA System Organ Class and Preferred Term: All Patients in Monotherapy Studies (Safety Population)

MedDRA SOC Preferred Term	STML-401-0114 (BPDCN) (N=47) n(%)	STML-401-0114 (AML) (N=49) n(%)	STML-401-0214 (N=16) n(%)	STML-401-0314 (N=29) n(%)	Total (N=141) n(%)
Investigations	0	2 (4.1)	0	0	2 (1.4)
Blood creatinine increased	0	1 (2.0)	0	0	1 (0.7)
Weight increased	0	1 (2.0)	0	0	1 (0.7)
Metabolism and nutrition disorders	1 (2.1)	2 (4.1)	1 (6.3)	1 (3.4)	5 (3.5)
Hyperkalaemia	0	0	0	1 (3.4)	1 (0.7)
Hypoalbuminaemia	1 (2.1)	2 (4.1)	1 (6.3)	0	4 (2.8)
Nervous system disorders	0	0	0	2 (6.9)	2 (1.4)
Cerebrovascular accident	0	0	0	2 (6.9)	2 (1.4)
Renal and urinary disorders	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Acute kidney injury	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Urinary tract disorder	0	0	0	1 (3.4)	1 (0.7)
Vascular disorders	0	1 (2.0)	0	1 (3.4)	2 (1.4)
Capillary leak syndrome	0	1 (2.0)	0	0	1 (0.7)
Hypotension	0	1 (2.0)	0	0	1 (0.7)
Shock haemorrhagic	0	0	0	1 (3.4)	1 (0.7)

Adverse Events Leading to Tagraxofusp Dose Interruption among All Patients in the Summary of Clinical Safety Pool

More than half (80 patients; 57%) of the 141 patients in the SCS pool had a dose interruption for the management of a TEAE, with the most common TEAEs leading to interruption being weight increased (25 patients; 18%); hypoalbuminaemia (20 patients; 14%); AST increased and pyrexia (each16 patients; 11%); ALT increased (13 patients; 9%); and CLS (10 patients; 7%). All other TEAEs leading to tagraxofusp dose interruption occurred in ≤5% of patients.

TEAEs leading to dose interruption were more common at a dose of 12 µg/kg/day (64% [72/113]) than at doses of 7 and 9 µg/kg/day (24% [5/21]).

Adverse Events Leading to Tagraxofusp Dose Reduction among All Patients in the Summary of Clinical Safety Pool

Only 3 (2%) of 141 patients in the SCS pool having a dose reduction. TEAEs resulting in a tagraxofusp dose reduction, each reported for 1 (1%) patient included multiple sclerosis relapse, neutropenia, thrombocytopenia, and pyrexia, with each of these events considered by the Investigator to be tagraxofusp-related, and transient ischaemic attack, which was considered unrelated.

Additional information

Additional data from stage 4 of trial 0114

Updated safety data from stage 4 of trial 0114 has been provided. Overall, 44 patients with BPDCN were treated with tagraxofusp; 42 of these received a lyophilized formulation and 2 patients received a frozen formulation. Safety data was presented by formulation and line of therapy (FL and R/R). Only data from BPDCN patients were included in the presented pools.

Summary tables included most common TEAES (≥10% of patients), treatment-related TEAEs, most common (≥ 5%) grade ≥ 3 TEAEs, all treatment-related grade ≥ 3 TEAEs, AESIs, and SAEs.

Fewer patients receiving lyophilized DP experienced TEAEs which may be considered signs and symptoms of CLS compared to the liquid formulation, such as hypoalbuminemia (45% vs 55%), peripheral oedema (31% vs 51%), weight increased (31 % vs 38%), hypotension (19% vs 28%). However, similar proportions in both pools had a diagnosis of CLS (21% vs 19%, respectively), all of which were considered related to treatment with tagraxofusp. Similar proportions experienced grade ≥ 3 CLS in both pools (10% vs 6%, respectively). More patients in the lyophilized pool experienced a SAE of CLS compared to the liquid formulation (17% vs 9%). This may be a reflection of higher vigilance by the investigators in Stage 4 of the trial, resulting in prolonged hospitalizations due to CLS, considering the emerging safety profile of tagraxofusp.

Five patients in Stage 4 treated with the lyophilized formulation of tagraxofusp, died from a TEAE. These were: 2 events of myocardial infarction, 1 event of CLS, 1 event of intracranial haemorrhage, 1 event of lung infection. Two of these deaths were considered treatment-related by the investigator: one case of CLS and one case of myocardial infarction concurrently with CLS.

Post marketing experience

Tagraxofusp was authorised in the US for the treatment of BPDCN (first-line and R/R) for adult and paediatric patients 2 years of age and older in December 2018. Since then and through March 2020, 97 patients were treated with tagraxofusp by 80 individual prescribers. In addition, tagraxofusp is available outside the US via an Early Access Program (EAP), under which 18 patients have been treated with tagraxofusp by 16 individual prescribers (all in the EU).

Safety data are collected as part of routine pharmacovigilance. Key safety data through April 2020 are summarised:

- 79 individual case study reports (ICSRs) have been submitted.
- The most commonly reported toxicity was CLS (22 individual cases, representing 28% of reported cases). Pyrexia, decreased albumin and increase in hepatic enzymes (8 cases each, 10% of reports cases) were also commonly reported.
- 39 ICSRs were assessed as serious.

- Ten cases had fatal outcomes, of which 6 were reported in patients experiencing CLS (the remaining 4 were in patients experiencing tumour lysis syndrome [n=2] and disease progression [N=2]). If considering all fatal cases in which CLS was reported as death due to CLS, the rate of fatal CLS is approximately 5%, consistent with the rate of fatal occurrences during clinical trials.

- Risk mitigation procedures recommended in the US label and proposed for the SmPC are effectively employed in the post-authorisation setting, minimising the risk of fatal events.

Table 98 provides a summary of common adverse events reported as ICSRs from US post-approval and early access programme (EAP) from December 2018 through March 2020 (incidence is based on the number of unique case IDs (N=79), not number of patients treated.

Table 98. Common Events Reported as ICSRs From US Post-approval and EAP

SOC	Preferred Term	N (%)
Blood and lymphatic system disorders	Thrombocytopenia	6 (8)
Cardiac disorders	Atrial fibrillation	4 (5)
General disorders and administration site conditions	Asthenia	5 (6)
	Fatigue	4 (5)
	Malaise	4 (5)
	Pyrexia	8 (10)
Infections and infestations	Sepsis	4 (5)
Investigations	Blood albumin decreased	8 (10)
	Hepatic enzyme increased	8 (10)
	Liver function test increased	7 (9)
	Platelet count decreased	4 (5)
Metabolism and nutrition disorders	Tumour lysis syndrome	4 (5)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	6 (8)
	Hypoxia	4 (5)
Vascular disorders	Capillary leak syndrome	22 (28)

2.6.1. Discussion on clinical safety

Safety results of tagraxofusp in BPDCN population are mainly coming from the study STML-401-0114 (study 0114). Supportive safety data from studies 0214 (for adverse risk AML), 0314 (for advanced high-risk myeloproliferative neoplasms) and 0414 (for R/R multiple myeloma) have been provided. All these studies are Phase I/II open-label and one-arm treatment. Therefore, there is no available data of tagraxofusp compared to other available therapies.

Summary of Clinical Safety (SCS) pool included data from studies 0114, 0214 and 0314. Among all Applicant-Sponsored Studies, a total of 141 patients received tagraxofusp as monotherapy (SCS pool); from these, only 113 patients received tagraxofusp at the intended dose (12 µg/kg/day). Overall, 96 patients were enrolled in the study 0114; 47 BPDCN (32 first-line and 15 R/R) and 49 AML patients. From these BPDCN patients, 3 first-line BPDCN patients received tagraxofusp at 7 µg/kg/day, 29 first-

line BPDCN patients received tagraxofusp at 12 µg/kg/day, and 15 R/R BPDCN patients received tagraxofusp at 12 µg/kg/day.

According to data provided from study 0114, median duration of exposure to tagraxofusp was 96 days (approximately 3.2 months) and 48 days (approximately 1.6 months) for first-line and R/R BPDCN, respectively. The median number of started cycles were 5.0 cycles and 3.0 cycles for first-line and R/R BPDCN, respectively. The median relative dose intensity was 98.71% for first-line BPDCN patients and 92.00% for R/R BPDCN patients.

Two different pharmaceutical forms (solution vs lyophilized powder) were administered to the full study population.

At DCO, 2 (4.3%) first-line BPDCN patients were still ongoing on treatment at study 0114. The primary cause for treatment discontinuation was disease recurrence/progression (48.9% for BPDCN and 51.0% for AML patients); this is in line with the results of study 0214 (56.3%) and study 0314 (34.5%). Discontinuation due to AEs was only a 4.3% (2/47) for BPDCN patients at study 0114.

The majority of the enrolled BPDCN population were males (83.0%). Asian (4.3%), black (0%) or other (2.1%) race were poorly represented within the study population. Median age was 69.0 years old (range 22 – 84 years old). All the BPDCN patients presented an ECOG PS score between 0 (46.8%) and 1 (53.2%). The demographic and baseline characteristics of the patients included are considered as well representative of the BPDCN patients excluding the race distribution.

All the BPDCN patients in the study 0114 reported a TEAE during the study and 87.2% of the total (87.5% first-line and 86.7% R/R BPDCN) reported TEAEs were considered drug-related. Moreover, higher percentage of R/R vs first-line BPDCN patients reported Grade ≥3 TEAEs (86.7% vs 78.1%) and SAEs (66.7% vs 40.6%). Tagraxofusp TEAE leading to discontinuation was only reported in 3.1% of the first-line BPDCN patients and in none of the R/R BPDCN patients (0%). TEAE leading to death were equally reported in both populations (6.3% first-line and 6.7% R/R). These results were generally in line with data provided from other studies.

Most common (≥20%) TEAEs in all the BPDCN population were ALT increased (63.8%), AST increased (59.6%), hypoalbuminaemia (55.3%), oedema peripheral (51.1%) and thrombocytopenia (48.9%), fatigue (44.7%), pyrexia (44.7%), nausea (46.8%), weight increased (38.3%), hyperglycaemia (36.2%), chills (34.0%), hypotension (27.7%), headache (25.5%), decrease appetite (25.5%), back pain (25.5%), anaemia (23.4%), constipation (23.4%), hypocalcaemia (23.4%), hypokalaemia (21.3%) and hypertension (21.3%). Results were mostly in line with the ones obtained for the SCS pool.

Results of TEAEs reported by ≥10% of patients in the SCS pool by cycle showed that in most of the cases AEs were reported with higher frequency and intensity in cycle 1 and 2 than in cycle 3 and beyond.

Overall, 87.2% (41/47) of the BPDCN patients reported at least one **treatment-related TEAE**. The most common reported tagraxofusp-related TEAEs (>20%), as assessed by the Investigator, occurring in all the BPDCN population were hypoalbuminaemia (51.1%), ALT increased (51.1%), AST increased (51.1%), thrombocytopenia (36.2%), pyrexia (29.8%), weight increased (27.7%), chills (27.7%) and nausea (23.5%). Results were mostly in line with the ones obtained for the SCS pool.

Grade ≥3 TEAEs were reported at least once for 80.9% (38/47) of the total of the BPDCN patients. The most common ≥Grade 3 TEAEs reported were thrombocytopenia (31.2%), ALT increased (24.8%), AST increased (24.1%) and anaemia (19.9%). Results were similar for the patients of the SCS pool.

SAEs were reported at least once in 48.9% (23/47) of the BPDCN patients. The most common reported TESAEs were Capillary leak syndrome (8.5%), pyrexia (6.4%), AST increased (4.3%) and

hypertension (4.3%). Overall, 57.4% (81/141) patients in the SCS pool reported at least one TESAEs and 26% (36/141) were considered as related to tagraxosfusp. Tagraxofusp-related SAEs reported for >1 patient included CLS (16 patients; 11%); febrile neutropenia (3%); AST increased (2%); and IRR, pyrexia, and pulmonary oedema (each 2%).

Among all the BPDCN patients, 3 cases of **Grade 5 TEAE**s/deaths were reported; 2 cases of CLS in first-line patients as tagraxofusp-related and 1 case of respiratory failure in R/R reported as not related. In the SCS pool, 11% (16/141) of the patients experienced at least one Grade 5 TEAEs. Among all the cases, 3 cases of CLS and one case of cerebrovascular accident were assessed by the Investigator as tagraxofusp-related. All other Grade 5 TEAEs were considered unrelated.

TEAE leading to dose discontinuation was reported in 2% (1/47) in the full BPDCN population and 11% (15/141) of patients in the SCS pool discontinued tagraxofusp because of a TEAE. Overall, 68.1% of all the BPDCN patients reported any **TEAE leading to dose interruption** (80/141 patients; 57% in the SCS pool) and 2.1% reported any **TEAE leading to dose reduction** (3/141 patients; 2% in the SCS pool).

AESIs

Liver transaminase Elevations - ALT and AST elevations were reported as adverse reactions in 46% (62/134) and 44% (60/134) of patients treated with Elzonris monotherapy, respectively. ≥ Grade 3 ALT and AST increased were reported in 23% (31/134) and 22% (30/134), respectively. Elevated liver enzymes occurred in the majority of patients in cycle 1 and were reversible following dose interruptions. Similar onset time and incidence were observed in patients with BPDCN, with 51% (24/47) of patients experiencing adverse events of ALT and AST elevations, with 34% (16/47) being ≥ Grade 3. Two patients with BPDCN met the laboratory criteria for Hy' s Law; in both cases the laboratory abnormalities were noted during Cycle 1.

In addition, two first-line BPDCN patients in this study met the laboratory criteria for Hy's Law but none of the cases were considered treatment-related by Investigator. Overall, 21.3% (10/47) presented Grade 1 ALP increased and, approximately, 8/47 patients (17%) presented TBL increased.

Capillary Leak Syndrome was reported in 17% (23/134), with 12% (16/134) Grade 2, 3% (4/134) Grade 3, 1% (1/134) Grade 4, and fatal in 1% (2/134). Of the 22 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 2 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 (19%, 9/47), including 13% (6/47) Grade 2, 2% Grade 4 (1/47) and 2 fatal cases (4%).

Similar CLS mitigation strategies as those included in the clinical trial protocols for tagraxofusp have been incorporated in the proposed SmPC. These include requirement for in-patient administration of the first cycle of tagraxofusp and CLS management guidelines including requirement for adequate cardiac function and serum albumin before initiating therapy; monitoring of signs/symptoms of CLS during dosing and recommendations for treatment interruptions; albumin supplementation in case of reduced serum albumin levels (see also the discussion on updated safety data below).

Clinical Signs and Symptoms of Capillary Leak Syndrome

Hypoalbuminaemia was reported at least once in 55.3% (24/47) of all BPDCN patients. Events were < grade 3 and non-serious and maximal shift observed in albumin levels from intensity Grade 0 or 1 was Grade 2; only one case lead to discontinuation. Incidence was higher at cycle 1 and lower thereafter. Albumin supplementation was common (64% [30/47]). In the clinical trials, 42% of patients overall

received albumin supplementation in cycle 1 of treatment. Findings for hypoalbuminaemia in the SCS pool were similar to those among BPDCN patients.

The study protocol for the main study 0114 has evolved from the earlier versions, where albumin supplementation was recommended if serum albumin < 3.0 g/dL, and threshold for withholding dosing was < 2.7 g/dL, and to recent versions, where supplementation is recommended at albumin levels < 3.5 g/dL, and threshold for withholding dosing is set to < 3.2 g/dL or 0.5 decrease from baseline in current cycle. Thus, it is anticipated that even higher proportions of patients will be needing albumin infusions according to the SmPC management guidelines, and more patients will have treatment interruptions. Theoretically, the use of albumin for prevention of CLS in tagraxofusp-treated patients with low or decreasing albumin levels can be understood based on the reverse oncotic effect and the potentially longer residence time in serum compared to saline. The mitigation strategy included in the proposed SmPC is supported.

Haematologic TEAEs - Any blood and lymphatic system disorders were reported in at least 68.1% (32/47) of all BPDCN patients. Events as thrombocytopenia, anaemia and neutropenia were experienced at a higher incidence by first-line compared to R/R patients, whereas, event as febrile neutropenia, leucocytosis, leukopenia and lymphopenia presented a higher incidence in R/R population. The most common events were thrombocytopenia (48.9%), anaemia (23.4%) and neutropenia (17.0%). The majority of the thrombocytopenia events were grade 3 with a maximum shift to grade 4 (19.1%). The majority of the anemia events were grade less than 3. None of all the reported event led to discontinuation. Findings for haematologic TEAEs among all 141 patients in the SCS pool were similar to those among BPDCN patients;

Other events of interest were: **1) infusion related-reactions** [14.9% (7/47)]; **2) hypersensitivity reactions** [48.9% (23/47)], it was serious for 9 (6%) patients, including pneumonitis and respiratory failure (3 patients [2%] and 4 patients [3%], respectively) and single (<1%) cases of allergic transfusion reaction, angioedema, and rash; **3) tumour lysis syndrome** [11% (5/47)], the majority of these event were Grade ≥ 3 in intensity and serious; **4) eye disorders** [18% (26/141) - including blurred vision in 6% (8/141) and conjunctival haemorrhage in 4% (6/141); **5) veno-occlusive disease (VDO)** [11.5% (3/26 patients that underwent SCT)], 2 of these patients receiving alternate therapy before SCT; **6) choroid plexitis**, it was not monitored in study 0114 as no clinical findings consistent with this toxicity in study Study 50047 part A(only 45 patients were followed during 1 cycle of treatment).

Choroid plexitis is rare event difficult to identify in clinical practice with a potential fatal outcome that is not considered sufficiently followed during tragraxofusp clinical development (only 45 patients from D1-12 in 1 cycle of treatment). Due to non-clinical findings together with issues of clinical events on the CNS reported suggest that this risk of developing any disorders in the choroid plexus is not sufficiently characterised. It has been included as an important potential risk in the RMP and a non-clinical study is recommended to be performed. Further, close monitoring would be needed in the post-authorisation setting.

ECG findings

In total, six (4%) patients in the SCS pool had a TEAE of QT prolonged. The event was assessed as grade 3 intensity for 2 of the patients. No cases were serious or led to treatment discontinuation. 36% of patients had a cardiac related TEAE. 10% of patients experienced a tagraxofusp-related cardiac event, most commonly tachycardia (6%), and sinus tachycardia (3%). Serious tagraxofusp-related cardiac disorders were one case of ventricular fibrillation and one case of pericardial effusion (refer to section on SAEs).

From the 96 patients enrolled in study 0114, 85 patients were evaluable for **immunogenicity analysis**; 31 first-line BPDCN patients, 14 R/R BPDCN patients and 40 AML patients. Immune response to tagraxofusp was assessed using two immunoassays to detect; 1) reactivity directed against tagraxofusp (ADA – anti DT antibodies) and 2) reactivity against the IL-3 portion of tagraxofusp (AIA).

ADA Analysis

As expected, due to the high diphtheria vaccination rate of the population, 90% (28/31) and 93% (13/14) of the first-line and R/R BPDCN patients, respectively, were ADA-positive at baseline. Among them, results showed that; i) 21% (6/28) and 23% (3/13) of the first-line and R/R BPDCN patients, respectively, presented neutralising antibodies (NAb-positive) at baseline, ii) 96% (27/28) and 85% (11/13) of the first-line and R/R BPDCN patients, respectively, presented boosted ADA (≥ 100-fold titer increase) after being administered tagraxofusp, and iii) the maximum fold increased titer for treatment boosted-ADA for first-line BPDCN patients was of 100,000 and was reached at C2D15, C2D21 and C4D21; for R/R BPDCN patients was of 1.000.000 and was reached at C2D21.

Among the evaluable ADA-negative BPDCN patients at baseline (9% - 3/31 and 7% - 1/14, first-line and R/R, respectively), results showed; i) 100% of the first-line and R/R BPDCN patients presented boosted ADA after tragaxofusp, and ii) the maximal peak positive titer was reached at C2D15 for the all the BPDCN population.

Overall, all the BPDCN population presented ADA increased levels after the beginning of treatment; reported incidence of treatment-boosted + treatment-induced ADA [97% and 86% for first-line and R/R, respectively]. NAb-positive incidence after treatment were between 96% (27/28) and 92% (12/13), for first-line and R/R, respectively.

According to the presented data, the high ADA titer remained mostly stable over the following 5 cycles study course.

AIA Analysis

Almost all of the patients were AIA-negative at baseline; only 1 patient (7%) from the R/R BPDCN population was AIA-positive. Results showed similar results for both first-line and R/R BPDCN population with incidence of treatment-induced AIA [90 (28/31) first-line & 92% (12/13) R/R] and a maximum fold increased titer of 51200 that was reached at C3D15. Almost all the patients were AIA positive after treatment and results of total AIA Nab-positive incidence was little higher for first-line patients (27/28-96%) compared to R/R patients (10/13-77%).

The AIA titers increased through C3D15 and then generally remained stable over the study course for patients with BPDCN with some fluctuations in R/R BPDCN patients.

To conclude, due to the high diphtheria vaccination rate of the population, almost all the BPDCN patients were ADA-positive at baseline whereas almost all of the patients were AIA-negative at baseline. All the BPDCN population presented ADA & AIA increased levels after the beginning of the treatment. Most of ADA & AIA were neutralizing antibodies.

A post-hoc analysis was performed with several comparisons to assess the clinical impact of the immunogenicity profile of tagraxofusp. According to the results obtained, the applicant concluded that no efficacy or safety parameters analysed demonstrated a statistically significant result.

Tagraxofusp is apparently triggering heavy hypersensitivity-related reactions in the patients, like cytokine release syndrome; respiratory failure; rash (generalised / maculo-papular); wheezing; pruritus; angioedema; swelling face; and flushing. Capillary leak syndrome and tumour lysis syndrome may also be related to hypersensitivity and is relatively frequent in the Tagraxofusp safety population.

To be able to elucidate potential influence on safety, the applicant was asked to submit data from each patient on ADAs (anti-tagraxofusp and anti-hIL3; titres, neutralising activity, NAb positive or negative at baseline) correlated with adverse effects that potentially can be associated with hypersensitivity reactions (infusion–related reactions, acute reactions, delayed hypersensitivity reactions). No firm conclusion can be drawn as information provided for assessment regarding impact of the presence of anti-drug antibodies was inconclusive. The applicant concluded that this toxicity was not likely due to immune complex formation which is considered acceptable.

Updated safety data from stage 4 of trial 0114 has been provided. The safety profile of tagraxofusp appears similar in stage 4 compared to previously assessed data, even if both pharmaceuticals forms of tagraxofusp (liquid *vs* lyophilized) are not yet confirmed to be comparable. Some differences were noted that are not considered meaningful to discuss in detail. However, the updated safety data support an unfavourable toxicity profile of tagraxofusp. Deaths from CLS events continue to occur. A related death event of myocardial infarction concurrently with CLS was reported. The effectiveness of the measures to minimize the CLS risk is, thus, questionable as it seems not to prevent serious events of CLS to occur. Further, serious events in CNS with fatal outcome continue to occur. In this sense, a toxic effect of tagraxofusp on the plexus choroid cannot be dismissed.

Safety data from patients treated with the lyophilised formulation has not been yet assessed for ADRs frequency calculations.

Related to post-marketing data from US provided during the procedure, 97 patients were treated from tagraxofusp since December 2018 from 80 different prescribers. Additionally, 18 patients have been treated with tagraxofusp by 16 prescribers in EU by an early access program.

Overall, 79 ICSRs were submitted (68.7%); the most comment reported toxicities were CLS (22/79- 28%), pyrexia, decreased albumin and increased hepatic enzymes (8/79- 10%, each). Almost the half of these cases were serious (39/79- 49.3%). This seems to be a large number of reports considering the number of patients treated and indicates the severe safety profile of tagraxofusp. Overall, 10 cases led to a fatal outcome (12.7% - 10/79). From these fatal cases, 6 cases were due to CLS (6/79- 7.6%), 2 cases due to tumour lysis syndrome and 2 cases due to disease progression.

The proportion of deaths due to CLS post-marketing (6/115) was somewhat higher than what was seen in clinical trials (3/47). CLS does not seem to be manageable, as deaths do occur despite extensive risk mitigation procedures. The CLS management guidelines should be reviewed and suggestions should be provided as seemed not to prevent severe cases to occur according to post-MA data provided and the PASS results would not be available at short term (however, the issues identified in the application prevent recommending granting a marketing authorisation).

Besides, events which may be associated with CLS, such as pyrexia and decreased serum albumin, increases in hepatic enzymes and liver function tests were commonly reported post-marketing.

The proportion of deaths due to TLS seem to be also higher in the post-authorisation setting than in clinical trials (1/47); two fatal cases of TLS were reported post-marketing. The warning about TLS in SmPC section 4.4 should be updated to indicate that TLS may be fatal with tagraxofusp (however, the issues identified in the application prevent recommending granting a marketing authorisation).

In addition, four events of atrial fibrillation were reported. Atrial fibrillation is not currently included in the SmPC section 4.8 table over ADRs. The applicant was asked to clarify the causality assessment for these reports, and to include the event as an ADR, if relevant (however, the issues identified in the application prevent recommending granting a marketing authorisation).

In this sense, the safety profile of tagraxofusp seen in clinical trials could have been underestimated probably due to the limitations of the study design and the small sample size as evidenced by post-

marketing data.

Additional expert consultations

See the input from the SAG in the Discussion on clinical efficacy.

2.6.2. Conclusions on the clinical safety

Tagraxofusp showed an unfavourable safety profile with high incidence and high level of seriousness of the events reported, mainly related to hepatotoxicity, capillary leak syndrome and haematological abnormalities. Hypersensitivity reactions, fatigue, pyrexia and pain were also frequent adverse reactions to tagraxofusp.

Significant safety issues have been identified with tagraxofusp. Specifically, the potentially fatal adverse drug reaction capillary leak syndrome occurred frequently in the applicant-sponsored clinical trials. Overall incidence in the SCS pool to date is 18% of patients (26/141). Of the 26 CLS events, 9 patients (35%) experienced a grade $\geqslant$3 event. 3 of the 26 patients (11%) died from a CLS event. Although mitigation strategies were implemented in the protocols after the first death due to CLS, it has not proven to be entirely preventable, with more deaths occurring after implementation. Further, the impact of other potential risks, e.g. hepatotoxicity, excessive amount of antibodies (ADAs) which might lead to severe immunogenicity reactions, are still unknown.

Entire safety database is based on data from single-arm trials in different diseases. In this context, the causality of the adverse events is difficult to demonstrate as they can be due to the drug effect, disease, aging or other factors. Moreover, the total number in SCS pool was 141 patients and among them, there were only 47 BPDCN patients treated with tagraxofusp in solution form with limited follow-up period.

2.7. Risk Management Plan

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant declared that tagraxofusp has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers tagraxofusp to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

The purpose of the current submission is to seek marketing approval for Elzonris (Tagraxofusp) in the following indication:

Elzonris is indicated as a monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

3.1.1. Disease or condition

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as blastic Natural killer (NK) cell lymphoma is an exceedingly rare haematological disorder derived from the precursor of plasmacytoid dendritic cells (pDCs) currently categorized under acute myeloid leukemia (AML) and related precursor neoplasms in the 2008 World health organization classification. BPDCN is a rare hematologic malignancy, highly aggressive, rapidly progressive, with a complicated diagnosis, where no consensus of standard treatment and no approved therapies.

3.1.2. Available therapies and unmet medical need

Currently, there is no consensus regarding the optimal treatment modality for BPDCN. Several treatments, including multi-agent chemotherapy regimens, symptomatic approaches (e.g. local radiation), and intensive chemotherapy with allogeneic hematopoietic cell transplantation, are generally used to treat patients.

Although chemotherapy regimens used for acute leukemia or lymphoma are often effective at inducing an initial response, the duration of response is typically brief and recurrent disease is generally resistant to chemotherapy. While longer overall survival has been reported with allogeneic hematopoietic cell transplantation, especially in younger patients many relapses have been observed after such transplants.

Achievement of high rates of durable response in patients with BPDCN with a targeted agent with the potential for patients to be bridged to SCT, while avoiding the morbidity and mortality observed with chemotherapy regimens would be potentially very impactful in this disease.

3.1.3. Main clinical study

SL-401 in Patients with Acute Myeloid Leukemia (AML) or Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN).

The main evidence of efficacy of tagraxofusp in patients with BPDCN is derived from study 0114. This was a multistage, phase 1/2, nonrandomized, open-label, multicenter study of tagraxofusp in nine study centers in the US, in patients with BPDCN and AML initiated in June 2014 and is ongoing at the time of the submission.

Favourable effects

The study has reached its primary endpoint, among first-line BPDCN patients **in stage 3**, CR rate (CR + CRc) was 53.8% (7/13) (95% CI: 25.1% - 80.8%). From the 7 first-line BPDCN patients with BM disease at baseline, BMCR rate was 85.7% (6/7) (95% CI: 42.1% - 99.6%) and the median duration of the BMCR was not reached.

Moreover, among **all 29 first-line BPDCN patients** treated with tagraxofusp at 12 µg/kg/day, CR rate (CR + CRc) was 72.4% (21/29) (95% CI: 52.8, 87.3). These results were also supported by secondary endpoint:

i) the median duration of the CR that was not reached through a median duration of follow-up of 24.9 months (95% CI: 20.9, 30.6) for the updated time-to event analyses of 03 October 2018,

ii) among the 14 first-line BPDCN patients with BM disease at baseline, BMCR rate was 92.9% (13/14) (95% CI: 66.1% - 99.8%) and the median duration of the BMCR was not reached,

iii) almost half of the patients were bridged to SCT [44.8% (13/29)], of these, 10 (77%) were alive and still in response as of the updated time-to event analysis,

iv) median OS was 18.0 months (95% CI: 9.7- NE) with a 58.6% probability of survival at 18 months and median PFS was 7.3 months (95% CI: 4.3 - NE).

v) ORR rate was 89.7% (95% CI: 72.6, 97.8) with a median duration of OR of 24.9 months (95% CI: 2.5 - NE),

In addition, among the 13 patients who achieved an objective response but were not bridged to SCT (6 with CR, 3 with CRc, and 4 with PR), six (46%) were alive at the time of the first data cut-off, with survival ranging from 11 to 30 months, including two patients with long-standing and ongoing responses (24 and 37 months).

3.2. Uncertainties and limitations about favourable effects

The Study 0114 is a single-arm clinical trial with a low number of patients for the analysis population (29 first-line and 15 R/R). It is therefore difficult to draw any firm conclusions without a control arm. In the literature, recent studies have shown comparable efficacy results when first line BPDCN patients have been treated with chemotherapy regimens (Poret 2015 and Pemmaraju 2017). Still, comparison with external sources is questionable due to the lack of prospective studies, standard response criteria and analogous population. In addition, the robustness of the effect size is uncertain leading to a possible variability in results. A difference between CR rate in Stage 3 vs Stage 1/2 (53.8% vs 87.5%) was indeed observed without obvious explanation with regards to baseline data.

Tagraxofusp showed a high rate of patients bridged to SCT. No detrimental effect of tagraxofusp over the SCT. However, in the context of a single arm trial, it cannot be excluded that investigator's choice to proceed to HSCT was partly influenced by the knowledge of the type of treatment. The calculation of duration of responses was performed irrespectively whether a patient has undergone SCT or not; thus, the real duration of the responses due to tagraxofusp is still misled. Further, the effect on OS presented in CSR seemed to be driven by the SCT itself more than to the effect to tagraxofusp; median

OS results presented for patients that did not undergo a transplantation were similar to outcomes obtained with regular chemotherapy.

Regarding R/R BPDCN patients, the study 0114 was not designed to provide any conclusion on this population; no hypothesis, objectives or endpoints were planned for R/R BPDCN patients. Moreover, efficacy results did not reveal clear evidence of clinical benefit of the treatment with tagraxofusp in these patient but a positive trend; CR rate was 13.3% (2/15) (95% CI: 1.7% - 40.5%), ORR rate was 67% (10/15) (95% CI: 38.4% - 88.2%)with a median OR duration of 1.6 months (95% CI: 0.7 - 3.6) , only one patient was bridged to SCT, median PFS was 2.6 months (95% CI: 0.6- 3.6) and median OS was 7.1 months (95% CI: 4.1- 11.9).

3.3. Unfavourable effects

The total safety database for tagraxofusp consists of 239 patients, about half of these stemming from a less rigidly conducted investigator-sponsored trial (91 patients, including 10 patients with BPDCN).

The safety profile of tagraxofusp was largely similar in patients with haematological malignancies across the studied indications (mainly BPDCN and AML, with few patients included with diagnoses of other haematological neoplasms).

Most common (⩾20%) TEAEs in all the BPDCN population were ALT increased (63.8%), AST increased (59.6%), hypoalbuminaemia (55.3%), peripheral oedema (51.1%) and thrombocytopenia (48.9%), fatigue (44.7%), pyrexia (44.7%), nausea (46.8%), weigh increased (38.3%), hyperglycaemia (36.2%), chills (34.0%), hypotension (27.7%), headache (25.5%), decrease appetite (25.5%) , back pain (25.5%), anaemia (23.4%), constipation (23.4%), hypocalcaemia (23.4%), hypokalaemia (21.3%) and hypertension (21.3%). Results were mostly in line with the ones obtained for the SCS pool.

≥Grade 3 TEAEs were reported at least once for 80.9% (38/47) of the total of the BPDCN patients. The most common ≥Grade 3 TEAEs reported were thrombocytopenia (31.2%), ALT increased (24.8%), AST increased (24.1%) and anaemia (19.9%). Results were similar for the patients of the SCS pool.

Treatment-Emergent SAEs were reported at least once in 48.9% (23/47) of the BPDCN patients. The most common reported SAEs were Capillary leak syndrome (CLS) (8.5%), pyrexia (6.4%), AST increased (4.3%) and hypertension (4.3%). Overall, 57.4% (81/141) patients in the SCS pool reported at least one SAEs and 26% (36/141) were considered as related to tagraxosfusp. Tagraxofusp-related SAEs reported for >1 patient included CLS (16 patients; 11%); febrile neutropenia (3%); AST increased (2%); and IRR, pyrexia, and pulmonary oedema (each 2%).

Among all the BPDCN patients, 3 cases of **Grade 5 TEAEs** were reported; 2 cases of CLS in first-line patients as tagraxofusp-related and 1 case of respiratory failure in R/R reported as not related. In the SCS pool, 11% (16/141) of the patients experienced at least one Grade 5 TEAEs. Among all the cases, 3 cases of CLS and one case of cerebrovascular accident were assessed by the Investigator as tagraxofusp-related. All other Grade 5 TEAEs were considered unrelated.

TEAE leading to dose discontinuation was reported in 2% (1/47) in the full BPDCN population and 11% (15/141) of patients in the SCS pool discontinued tagraxofusp because of a TEAE. Overall, 68.1% of all the BPDCN patients reported any **TEAE leading to dose interruption** (80/141 patients; 57% in the SCS pool) and 2.1% reported any **TEAE leading to dose reduction** (3/141 patients; 2% in the SCS pool).

Events as liver transaminase elevations, capillary leak syndrome and haematologic TEAEs were considered as **AESIs**. Other events of interest were: infusion related-reactions, hypersensitivity reactions, tumor lysis syndrome, eye disorders, veno-occlusive disease and choroid plexitis.

3.4. Uncertainties and limitations about unfavourable effects

Entire safety database is based on data from single-arm trials in different diseases. In this context, the causality of the adverse events is difficult to demonstrate as they can be due to the drug effect, disease, aging or other factors. Thus, weighing the safety profile of tagraxofusp against other chemotherapy treatments currently used for treatment of BPDCN is difficult.

Moreover, the total number in SCS pool was 141 patients and from them, there were only 47 BPDCN patients with limited follow-up period. The small size of the safety database adds uncertainty to the frequency estimates for the observed adverse effects, and ADRs with lower frequencies may not have been observed, or may not have been correctly attributed to the true cause. The relatively short follow-up time is a limitation to discern potential long-term effects of tagraxofusp. Therefore, the safety profile of tagraxofusp could remain uncertain due to the lack of information. Safety due to long-term exposure is still uncertain as the median duration of exposure were 5 cycles (96 days) in first-line and 3 cycles (48 days) in R/R BPDCN patients and there is evidence of 2 patients treated for more than 20 cycles that reported a high number of TEAEs after cycle 4.

Within the safety reporting period of 30 days after the last dose of tagraxofusp in the applicant-sponsored studies, sixteen (11%) deaths occurred in the SCS pool; 12 of them occurred within the 10 days after dosing. Due to the scarcity of information about the events, and lack of applicant discussion of the causality assessment, the extent to which treatment with tagraxofusp may be fatal is still uncertain. For the purpose of estimating tagraxofusp-related mortality, considering the very small number of BPDCN patients in the clinical trials, the entire tagraxofusp-treated patient population should Have been taken into account even if these events were classified as unrelated.

The most important uncertainties about the unfavourable effect are related to risk of: i) capillary leak syndrome, associated with an apparent insufficient management algorithms for minimisation, ii) hepatotoxicity, with a high frequency of increased ALT and AST events, 2 identified cases of Hy's law and an uncertain risk of DILI. In addition, choroid plexitis, which is a rare event difficult to identify in clinical practice with a potential fatal outcome that is not considered sufficiently followed during tragraxofusp clinical development (only 45 patients from D1-12 in 1 cycle of treatment). Non-clinical findings together with issues of clinical events on the CNS reported suggest that this risk of developing any disorders in the choroid plexus is not sufficiently characterised and close monitoring would be needed in the post authorisation setting. The risks of 'hypersensitivity', 'haematological abnormalities' and 'tumour lysis syndrome' are considered sufficiently characterized. However, these undesirable clinical outcomes will have to be closely followed in the PSUR.

In relation to the immunogenic profile of tagraxofusp, the clinical impact on safety of the presence of antidrug antibodies, ADA (anti-DT antibodies) & AIA (anti-IL3 antibodies), is still uncertain. Despite toxicity seemed not to be likely related to the immune complex formation as it is mostly reported in cycles 1 and 2, the high titer of ADA and AIA that was observed during the full treatment course of tagraxofusp and the limited safety data on long-term exposure did not allow to draw any firm conclusion. According to data provided from the post-authorisation setting, the safety profile of tagraxofusp seen in clinical trials could have been underestimated probably due to the limitations of the study design and the small sample size. Further, the high rate of deaths due to CLS reported in the post-marketing setting called into question the RMM for this risk.

3.5. Effects Table

Table 99. Effects Table for tagraxofusp in all patients with first-line BPDCN (data cut-off: 31 Jan 2018).

Effect	Short Description	Unit	Tagraxofusp	Control	Uncertainties/ Strength of evidence
Favourable Effects					
CR/CRc* Rate	Includes all stages	N (%) (95% CI)	21 (72.4) (52.8, 87.3)	N/A	Heterogeneous response rate in the different cohorts and so robustness of the effect size
Median Duration of CR/CRc	Includes all stages	months	Not Reached	N/A	
Bridge to Stem Cell Transplant Rate	Includes all stages	N (%)	13 (44.8)	N/A	Whether or not influenced by the knowledge of the type of treatment
Unfavourable Effects					
TEAEs	regardless causality	%	100	N/A	
TEAEs Grade ≥ 3	regardless causality	%	80.9	N/A	
Serious AEs	regardless causality	%	48.9	N/A	
TEAEs leading to discontinuation	regardless causality	%	2.1	N/A	
TEAEs leading to reduction	regardless causality	%	2.1	N/A	
TEAEs leading to interruption	regardless causality	%	68.1	N/A	
TEAEs leading to death	regardless causality	%	6.4	N/A	
CLS		%	17%	N/A	Whether or not management algorithms for minimisation are insufficient

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Efficacy results obtained for first line BPDCN population, including patients from all stages, showed a high rate of complete responses (72.4%, median duration not reached) with a high percentage of patients that achieved bone-marrow complete response. Retrospective studies suggest that induction therapy with regimens commonly used in non-Hodgkin lymphoma, AML and ALL yield high response rates (CR of 40-90%). Still, the limited information in the literature on outcome with currently used chemotherapies in BPDCN do not allow contextualisation of the CR rate, DOR and SCT rate reported in study 0114.

The number of patients bridged to SCT in study 0114 is high, but in the context of a single arm trial, it cannot be excluded that investigator's choice to proceed to HSCT was partly influenced by the knowledge of the type of treatment. Contextualisation of this outcome with historical/near-

contemporary controls was not feasible. In non-transplanted patients, two observations (out of 16) showed unusual prolonged responses, possibly indicating a benefit even without transplantation. However, median OS results presented for patients that did not undergo a transplantation were similar to outcomes obtained with regular chemotherapy.

These effects are however observed in a small single-arm trial limiting the robustness of the results. Responses unequivocally show the activity of tagraxofusp, even in such a non-comparative setting. Many factors of confusion (such as specifics of the included population, external factors contributing to outcomes) render the effects on more relevant endpoints (DoR, proportion of patients amenable to transplantation, OS) less certain and of disputable interpretation. Further, supportive efficacy data from stage 4 did not bring reassurance as a lower efficacy profile in the target population was shown.

In relapse or refractory patients, the very limited set of exploratory data probably prevents any firm conclusion on a clinical benefit. Further, R/R patients may represent a different population in terms of phenotype expression and the loss of target expression (CD123) was not investigated.

Tagraxofusp showed an unfavourable safety profile with high incidence and high level of seriousness of the events reported, mainly related to hepatotoxicity and capillary leak syndrome. Many treatment interruptions could indicate that this treatment presents a poorly manageable safety profile. The safety profile of tagraxofusp is different compared to intensive chemotherapy; while hypersensitivity reactions and potentially fatal AEs like CLS were related to tagraxofusp, the rate of haematological toxicity seems to be a limited problem. Further, the effectiveness of the algorithms for risk minimization and the impact of other potential risks are unknown.

Moreover, it is of concern that overall 11% of patients in the pooled safety population died within one month after dosing with tagraxofusp; most worrisome is the potentially fatal adverse drug reaction CLS, which occurred frequently in the applicant-sponsored clinical trials. Indeed, post authorisation safety data provided showed unfavourable safety profile of tagraxofusp and called into question the risk minimisation measures for CLS as a high rate of death due to this type of events were reported.

3.6.2. Balance of benefits and risks

Due to limitation in the study design, methodological issues, uncomprehensive efficacy results and uncertainties on the management of the safety profile the overall Benefit/risk of tagraxofusp is negative.

3.6.3. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The overall B/R of tagraxofusp in the intended indication is considered negative.

Divergent positions are appended to this report.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Elzonris as a monotherapy in the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), the CHMP considers by majority decision that the safety and efficacy of the above mentioned medicinal product

is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

In the context of a one-pivotal-trial scenario, the evidence in support of the claimed indication of tagraxofusp as monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) is considered insufficient:

- The pivotal 4 cohort phase I/II study has important limitations rendering the benefit of tagraxofusp not robustly demonstrated in the context of a single pivotal trial with a non-randomised design and a small sample size. A total of 84 BPDCN patients (n=65 first line and n=19 second line) have been enrolled.
- Statistical analysis was only planned for cohort 3 of the study in which a total of 13 first line patients were enrolled. Study 0114 was thus not designed to detect a particular magnitude of effect in the BPDCN population as studied.
- Pivotal efficacy results showed an anti-disease activity in cohort 3 with a complete response rate (CR/CRc) of 53.8%. However:

  i) The magnitude of the efficacy response was highly heterogeneous across the 4 stages;

  ii) It is not clear why CR rate and HSCT decreased over time in the successive cohorts;

  iii) The activity seen in second line are unlikely to represent benefit for the second line population;

  iv) The safety profile is not well characterized.
- Therefore, taking into account these concerns in the context of a limited and heterogenous dataset, the CHMP cannot conclude that efficacy has been robustly shown. Together with the uncertainties on the safety profile, B/R cannot be established.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant’s claim of new active substance status, the CHMP position at the time of this report is reflected in section 2.9 (new active substance). However, in light of the negative recommendation, the CHMP is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Divergent position(s) to the majority recommendation are appended to this report.

5. Re-examination of the CHMP opinion of 23 July 2020

Following the CHMP conclusion that Elzonris was not approvable based on the efficacy and safety grounds outlined above, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation the following detailed grounds for re-examination.

A summary of the applicant's grounds for re-examination is presented below.

Ground for refusal number 1

The pivotal 4 cohort phase I/II study has important limitations rendering the benefit of tagraxofusp not robustly demonstrated in the context of a single pivotal trial with a non-randomised design and a small sample size. A total of 84 BPDCN patients (n=65 first line and n=19 second line) have been enrolled.

Ground for re-examination number 1

Applicant study 0114 was the first prospective clinical trial in BPDCN. This was a well-designed, multi-cohort single-arm trial (SAT) conducted over 6 years, representing exploratory, confirmatory and open-access phases of drug development. Although SATs are not always adequate, the applicant has considered that SATs have successfully established efficacy in other haematological or rare disease indications. The reasons why a SAT was considered appropriate for this submission is discussed below, together with the adequacy of the sample size and robustness of the data produced.

Single-arm Design

Control arms in clinical trials, with allocation of patients to treatments by randomisation, are particularly important when baseline factors are prognostic for outcomes and, related to this, where the response to control is not fully predictable. Randomisation promotes balance in prognostic factors (and unmeasured confounders) between treatment groups and is important when needing to set an index date (e.g. to measure time to event variables). Thus, randomisation to allocate patients to different treatment arms is important for the majority of trials. However, these considerations do not apply to the assessment of complete response in haematology trials, in which response in the absence of treatment is fully predictable.

A SAT was therefore considered appropriate to provide the evidence of treatment efficacy in BPDCN, given that the direct therapeutic effect of an intervention can be measured by achievement of complete disease remission. CR/CRc is the maximal therapeutic response that can be achieved and does not occur spontaneously, i.e. without an effective intervention. Furthermore, the importance of complete response to an individual patient with BPDCN is well characterized. Complete response shows not only direct evidence of treatment efficacy in an individual patient, but is an appropriate variable on which to quantify the magnitude of the beneficial effect across a population, wherein all complete responses can be attributed to a drug effect; hence a control arm is not required. Other important efficacy variables, such as duration of response, can only be assessed in a cohort of patients in which a remission is induced; a naïve comparison between durations of remission in patients achieving remission on treatment and patients achieving remission on a control arm would anyway not describe a treatment effect. This point provides further rationale for the decision to use a SAT.

The applicant maintains that the beneficial effects of treatment can be established and quantified based on a SAT.

Robustness of Trial

Specific measures and procedures were implemented to ensure the robustness of the clinical dataset:

- Inclusion / exclusion criteria were prospectively defined and consistent across study stages except for Stage 3, that by definition, only enrolled first-line patients.
- All patients with BPDCN enrolled in the trial were required to have histologically and/or cytologically-confirmed BPDCN by pathologic assessment according to the 2008 WHO classification by a pathologist with expertise in haematologic malignancies.
- Pathology material was submitted for review by a central pathologist for confirmation of the diagnosis of BPDCN, and this confirmation was required for a patient to be included in the efficacy analysis.
- Baseline disease was thoroughly assessed by bone marrow biopsy/aspirate, computed tomography (CT) scans for lymphadenopathy and visceral disease, blood sampling for peripheral blasts and cytopenias, and the modified severity-weighted assessment tool (mSWAT) and skin biopsy for evaluation of skin disease.
- Stringent response criteria considering all disease manifestations were developed in collaboration with medical experts in BPDCN. Based on these criteria, CR required normalisation of blast percentage in the bone marrow, normalisation of absolute neutrophil and platelet counts, absence of leukemic blasts in the peripheral blood, 100% clearance of all skin lesions present at baseline, regression of nodal masses to normal size on CT scan, and nonpalpable spleen/liver with no nodules. As part of the response criteria, a new response designation, clinical CR (CRc) was introduced to describe a specific response to treatment that included all the features of a CR in non-skin sites of disease, with the skin having clinically inconsequential residual skin abnormality, that would not clinically be considered active disease (CRc was validated prior to its inclusion in the primary efficacy analysis).

Furthermore, the included patients had similar demographics and baseline characteristics to what is seen in the real-world setting, rendering the results relevant to the intended population.

As a result, the clinical dataset generated in this study is robust and enables an assessment of the benefit of tagraxofusp in the intended population.

Sample Size

The sample size is considered adequate to estimate the effects of treatment with sufficient precision to enable a benefit-risk assessment, with a lower bound of the 95% CI of 32.5% in the pooled data for Stages 3 and 4 and 44.0% for the pooled data cross all 4 stages of the trial.

Conclusions

In summary, complete response will not occur without effective treatment, regardless of the patient's pre-treatment demographic or clinical characteristics. As such, all complete responses seen can be attributed to tagraxofusp's effect, allowing the magnitude of effect to be assessed. This is a key point of why a SAT was considered appropriate. Additionally, the sample size is adequate to produce sufficient precision to enable a benefit-risk assessment. In theory, the sample size in the study would represent approximately 10-15% of the EU BPDCN ultra-rare population (Bueno, 2004; Wang, 2012) and the included patients had similar demographics and baseline characteristics to what is seen in the real-world setting, rendering the results relevant to the wider population.

Ground for refusal number 2

Statistical analysis was only planned for cohort 3 of the study in which a total of 13 first line patients were enrolled. Study 0114 was thus not designed to detect a particular magnitude of effect in the BPDCN population as studied.

Ground for re-examination number 2

As per the 0114 study design and pre-specified statistical approach, the treatment effect of tagraxofusp in first-line patients was estimated in 3 separate cohorts (Stages 1-2, Stage 3, and Stage 4), with efficacy confirmed in a prospectively designed pivotal stage (Stage 3).

The sample size for Stage 3 was calculated to provide at least 90% power at a two-sided Type I error rate of 0.05 to reject a null hypothesis that the rate of complete response (CR+CRc) was ≤ 10%, if the true rate was 60%. These assumptions were considered appropriate to enable an assessment of the efficacy of tagraxofusp given the knowledge that therapeutic intervention is an absolute requirement for achievement of any response in this disease (i.e. spontaneous disease remission cannot occur), and the substantial treatment effect required to reject the null hypothesis on the basis of that sample size.

Indeed, rejection of the null hypothesis for the primary endpoint in Stage 3 was achieved at the pre-specified significance level. Importantly, while a 10% rate of complete remission was used to define clinically meaningless efficacy for the purpose of sample size calculation (based on advice from medical experts in BPDCN and the lack of any authorised therapies or standard of care), the lower bound of the 95% confidence interval in each stage of the study was far higher than this, at > 25%, which cannot be considered a clinically meaningless rate. Although a statistical hypothesis was not pre-specified for the entire sample of 65 patients, the hypothesis test in Stage 3 was pre-specified to establish that a beneficial effect exists and the observed results, by stage or pooled, can be interpreted for assessment of the magnitude of that effect, with the pooled results allowing sufficient precision for an assessment of benefit-risk.

As previously discussed, patients with R/R BPDCN represent a population that is more difficult to treat and with worse prognosis than first-line patients. While no hypothesis testing was specified to estimate the magnitude of treatment efficacy in this population, the biological similarity of the disease to first-line patients render the therapeutic target, CD123, scientifically relevant and the observed results showed a treatment effect that is clinically meaningful given the very poor prognosis of this population and the unmet medical need.

Ground for refusal number 3

Pivotal efficacy results showed an anti-disease activity in cohort 3 with a complete response rate (CR/CRc) of 53.8%. However:

i) The magnitude of the efficacy response was highly heterogeneous across the 4 stages;

Ground for re-examination number 3

It is understood that the concerns expressed in Parts i) and ii) relate not to the meaningfulness of the observed CR/CRc rate per se, but to the perception that the percentage of responders (in first-line patients) varies across the different stages of the study and that a lower effect in Stage 4 presents uncertainties for the use of tagraxofusp in the real-world setting. Furthermore, it is also understood that the concern relates to both the primary endpoint of complete response rate as well as to the percentage

of patients who bridged to SCT. As i) and ii) are inextricably linked, the response below addresses them jointly.

Results in first-line patients for complete response and SCT rates are summarized in Table 100:

Table 100. Complete Response and Bridging to SCT Rates in First-Line BPDCN Patients Treated With 12 mcg/kg of Tagraxofusp

	Stage 1-2 (N=16)	Stage 3 (Pivotal) (N=13)	Stage 4 (N=36) [1]
CR/CRc, n (%)	14 (87.5)	7 (53.8)	16 (44.4)
95% CI	(61.7 , 98.4)	(25.1 , 80.8)	(27.9 , 61.9)
Bridged to SCT			
n (%)	7 (43.8)	6 (46.2)	8 (22.2)
Median Age (years)	65	61	58

Source: D180 Response to Question Table 18.3 D180 Response to Question 18.4

Complete Response Rate in First-Line Patients

The treatment effect is strong and clinically meaningful in all stages. The applicant acknowledges that the complete response rates in Stage 3 and Stage 4 are lower than in Stages 1 and 2. However, it is well-known in drug development that exploratory stages typically show higher treatment effects than later confirmatory stages. Thus, this was not unexpected and the treatment effect in Stages 3 and 4 was nonetheless strong with clinically meaningful complete response rates.

Furthermore, the complete response rates in Stage 3 and Stage 4 are similar (53.8% and 44.4%, respectively), as indicated by overlapping 95% CIs. The magnitude of response is clinically meaningful with acceptable precision as the lower bound of the 95% CI in each study stage is > 25%.

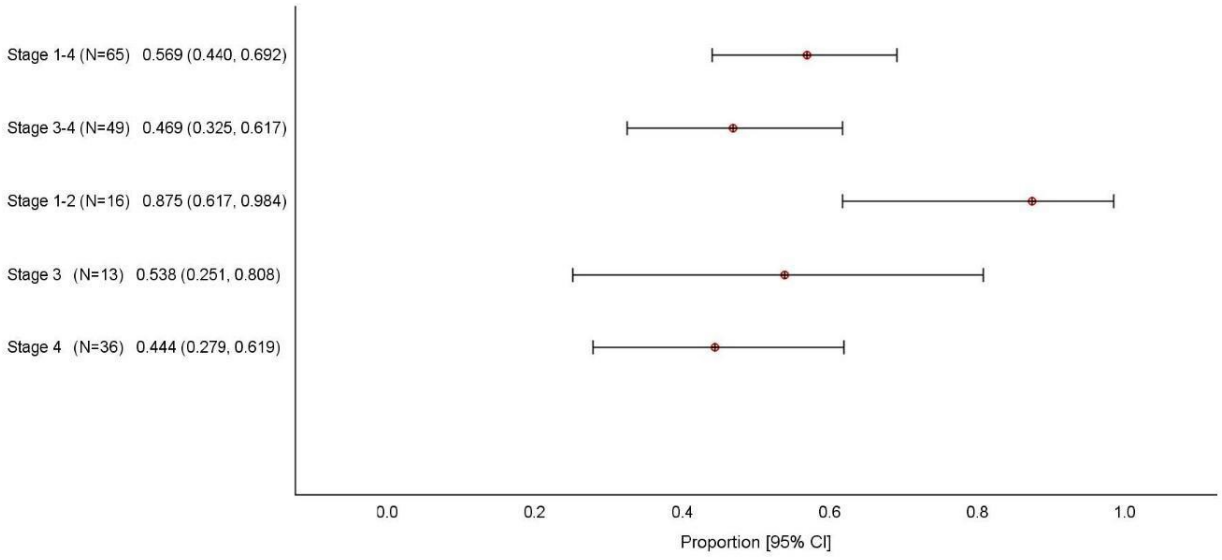


Figure 179: Rates of Complete Remission in Study 0114 (First-Line Patients)

The demographics/baseline characteristics of the patients in the 0114 clinical trial are consistent with the intended population to be treated in a real-world setting. As such, there is no basis to consider that complete response rates in the real-world setting will be lower than what has been seen in the 0114 clinical trial.

GfR number 3 ii) It is not clear why CR rate and HSCT decreased over time in the successive cohorts;

Percentage of First-Line Patients Who were Bridged to SCT

The percentage of patients who bridged to SCT was similar between Stage 1 and 2 and Stage 3 (43.8% in Stage 1and 2, 46.2% in Stage 3). However, despite similar complete response rates in Stage 3 and Stage 4, a difference in the percentage of patients bridging to SCT was observed (46.2% in Stage 3, 22.2% in Stage 4). The applicant considers that these differences in the proportion of patients with complete response versus the proportion bridging to SCT across the different stages are unrelated to the drug effect, especially as the protocol-defined criteria for meeting CR/CRc were identical across the different stages of the trial. A proposed explanation is that multiple confounding factors that influence whether a patient undergoes SCT, such as age, fitness, comorbid conditions, availability of a suitable transplant donor etc., may have led to the heterogeneity seen. The applicant recognizes that the decision to proceed to SCT is multifactorial and that SCT rates, while clinically important, are not a direct measure of the drug's magnitude of effect. However, CR provides direct evidence of a drug effect because all BPDCN patients have a disease in need of induction therapy as a first measure, prior to consideration for future transplant which requires induction-induced remission as a pre-requisite.

In summary, the complete response rate is a direct measure of tagraxofusp's effect and is the appropriate basis on which to estimate the magnitude of that effect. The aim of the study was to confirm and quantify a beneficial effect of the drug, and this was achieved as evidenced by the high complete response rates across all stages of the clinical trial. Differences in complete response or SCT rates across trial stages is not unexpected in cohorts that are not large in absolute terms. What is critical is that each stage and the pooling between stages established a relevant magnitude of effect for complete response rates to enable a benefit-risk assessment. The effects of tagraxofusp were demonstrated by the high complete response rates presented in this Response. Furthermore, duration of response was long enough to enable a substantial proportion of patients (32.3% [21/65] overall) to bridge to SCT, thereby providing further evidence of efficacy as all BPDCN patients need to achieve disease remission before proceeding to SCT.

GfR number 3 iii) The activity seen in second line are unlikely to represent benefit for the second line population

As broadly accepted in the acute leukaemia setting, patients with R/R BPDCN represent a population that is more difficult to treat and with worse prognosis than first-line patients. While research is ongoing to elucidate potential resistance mechanisms and other factors that result in worse outcomes for these patients, both newly-diagnosed and recurring BPDCN arise from proliferation of malignant pDCs that ubiquitously express CD123 at high levels, suggesting that CD123 is an important therapeutic target in both first-line and R/R patients (Togami, 2019; Angelot-Delettre, 2015; Haubner 2019); indicate that CD123 expression is present on BPDCN cells from both first-line and R/R patients, rendering treatment with tagraxofusp scientifically valuable . Furthermore, clinical benefit was observed in some patients as 3 (15.8%) patients achieved a complete response, one of whom bridged to SCT. Responses in the remaining 8 patients who achieved an objective response were Cri in 3 (15.8%) patients and PR in 5 (26.3%) patients. Median overall survival in the 19 R/R BPDCN patients was 8.2 months with a range of 0.6 to 27.1 months. It should be noted that some of the R/R patients were heavily pre-treated (i.e. this

group did not only include second-line patients) as 40% of patients had received two or more prior therapies; these patients, in particular, may be considered the most difficult to treat.

GfR number 3 iv) The safety profile is not well characterized

The applicant considers the safety profile of tagraxofusp has been characterized. This response provides a summary of the safety experience to date from the clinical trials and post-marketing US/EAP in Europe setting.

At the time of the MAA submission in January 2019, the safety database, in addition to the pivotal Study 0114 in BPDCN patients, included safety data from 3 other applicant-sponsored studies of tagraxofusp, in haematologic malignancies other than BPDCN:

- Study STML-401-0214 (study 0214), a Phase 1/2 non-randomized, open-label, 2-stage dose-escalation study of tagraxofusp as monotherapy in patients with adverse risk AML in first or second CR, with or without evidence of minimal residual disease in first CR.
- Study STML-401-0314 (study 0314), a Phase 1/2 non-randomized, open-label, 2-stage dose-escalation study of tagraxofusp as monotherapy in patients with advanced, high-risk myeloproliferative neoplasms.
- Study STML-401-0414 (study 0414), a Phase 1/2 non-randomized, open-label, 2-stage dose-escalation study of tagraxofusp in combination with pomalidomide and dexamethasone in patients with R/R multiple myeloma.

Overall, safety data from 148 patients treated in four clinical studies of tagraxofusp in haematologic malignancies (including study 0114) were included in the initial MAA (data cut-off 25 September 2017), primarily from 141 patients who received multi-cycle treatment with tagraxofusp as monotherapy. This included three first-line BPDCN patients who received tagraxofusp at 7 mcg/kg/day, 29 first-line BPDCN patients who received tagraxofusp at 12 mcg/kg/day as well as 15 R/R BPDCN patients who received tagraxofusp at 12 mcg/kg/day.

Subgroup analyses of the safety database looking at age, sex, weight and ECOG performance status revealed no major demographic differences across the subgroups and the demographic characteristics of the BPDCN patient population was consistent with that reported in the published literature.

As part of the responses to the Day 180 List of Questions, the applicant provided updated safety data from a total of 176 patients included in the monotherapy studies treated with tagraxofusp ≤ 12 mcg/kg including all 89 patients with BPDCN treated in Stages 1 through 4 of study 0114 (86 were treated at the to-be marketed dose of 12 mcg/kg/day), 42 patients with AML treated in study 0114, and 45 patients with haematologic malignancies treated in studies 0214 and 0314 (data cut-off June 2019).

These data were further supplemented by safety data from 'real-world' usage collected via routine pharmacovigilance from commercial supply in the US, where tagraxofusp has been licensed for the treatment of first-line and R/R adult and BPDCN paediatric patients 2 years of age and older since December 2018. Data from 110 US patients treated between December 2018 and June 2020 have been submitted, as well as safety data from 26 EU patients treated with tagraxofusp via an early access programme.

The applicant also plans to complement these data with a clinical Post-Approval Safety Study (PASS), the design of which was agreed with the Agency during review based on the main safety concerns associated with tagraxofusp use and is detailed in the Risk Management Plan. This non-interventional category 3 PASS has a primary objective to assess the incidence of capillary leak syndrome (CLS) in approximately 125 adult patients actively treated for BPDCN in routine practice in the EU compared to clinical studies. Secondary objectives currently include: (i) evaluation of the distribution of CLS severity;

(ii) evaluation of data on dose interruptions and/ or the administration of intravenous albumin supplementation in patients presenting with a diagnosis or symptoms of CLS (i.e. hypoalbuminemia, oedema, weight gain and/or hypotension); (iii) evaluation of the incidence and severity of hepatotoxicity in patients actively treated for BPDCN in routine practice and; (iv) describing the available safety data of tagraxofusp monotherapy in patients with significant cardiovascular history, hepatic impairment and/or severe renal impairment.

While the collection of further informative safety data are awaited, a number of measures are proposed which are designed to: (i) Restrict the usage of tagraxofusp to patients consistent with those studied in clinical trials who have sufficient cardiac, renal and hepatic function prior to treatment. Testing related to these parameters will be required before start of treatment and prior to each dose; (ii) Manage potential adverse reactions which primarily occur at the start of treatment by requiring tagraxofusp to be administered in an in-patient setting in cycle 1. Consistent with other biologic agents used in oncology, patients are to be pre-treated before each infusion to reduce risk of hypersensitivity and/or anaphylaxis and; (iii) Provide detailed safety information via routine pharmacovigilance with specific follow up questionnaires for renal, hepatic and cardiac events. In addition, the applicant will offer training to healthcare professionals to advise them before any tagraxofusp is given to the site's first patient.

Overall Safety Profile

Acceptable safety has been demonstrated in a sizeable dataset (up to June 2019) of 176 patients treated with monotherapy in clinical trials and an additional 128 patients treated in the post-marketing/EAP setting. Importantly, the post-marketing/EAP experience is thus far consistent with the adverse events seen in the clinical trials, especially with regard to CLS, which is the most important identified risk (discussed further below). The clinical trial data showed that most adverse events were transient, manageable and did not accumulate over cycles of therapy, and importantly, there was no prolonged myelosuppression. Notably, the safety profile in study 0114 was similar across older patients compared with middle-aged and younger patients.

Deaths

21 deaths occurred within 30 days of last tagraxofusp dose in the clinical studies (all dose, monotherapy). This is out of a total population of 190 treated patients (148 from original SCS population and 48 patients with BPDCN in Stage 4 of study 0114), up to June 2019. The death rate is thus 11%, which is lower than death rates of 17% and 26% reported in the literature with combination chemotherapy for BPDCN (Pagano 2013, Martin–Martin 2015). Four of the deaths were due to CLS, which equates to a CLS death rate of 2.1%. The bolded events in the 'Cause of Death' column were considered by the investigator to be treatment related.

In the US post-marketing/European EAP setting, there have been 10 ICSRs with a fatal outcome out of 128 patients treated to June 2020. This equates to a death rate of 7.8%. Four ICSRs indicated CLS as the cause of death. This equates to a CLS death rate of 3.1%, which is consistent with that seen in the clinical trial setting.

Table 101. Deaths Within 30 Days of Last Tagraxofusp Dose in Clinical Studies (N=190)

Pt. Number	Age/ Sex	Disease	Date of Diagnosis	Line	Prior treatment lines	Dose[1]	Treatment Start Date	Treatment End Date	Date of Death	Rel Day [1]	Cause of Death [2]
Study 0114											
[redacted]		BPDCN	2018-10-08	FL	0	12	2018-12-14	2018-12-18	2018-12-22	5	**Capillary leak syndrome**
[redacted]		BPDCN	2017-05-18	FL	0	12	2017-10-23	2017-10-28	2017-10-31	4	Myocardial infarction
[redacted]		AML	2013-04-09	R/R	3	16	2015-08-04	2015-10-04	2015-10-30	27	Intracranial haemorrhage
[redacted]		AML	2014-12-02	R/R	≥4	12	2016-01-25	2016-01-26	2016-02-22	28	Myocardial infarction
[redacted]		BPDCN	2014-09-09	FL	0	7	2014-11-03	2014-11-07	2014-11-21	15	**Capillary leak syndrome**
[redacted]		AML	2015-04-20	R/R	1	16	2015-07-27	2015-07-29	2015-07-31	3	**Capillary leak syndrome**
[redacted]		AML	2014-09-03	R/R	1	12	2016-03-24	2016-03-29	2016-04-07	10	lung infection; Pneumonia
[redacted]		BPDCN	2017-01	R/R	1	12	2018-01-30	2018-02-23	2018-03-09	15	Intracranial haemorrhage
[redacted]		BPDCN	2012-12	R/R	1	12	2018-05-12	2018-05-16	2018-06-13	29	Lung infection
[redacted]		BPDCN	2018-04-17	FL	0	12	2018-06-15	2018-06-18	2018-06-20	3	**Myocardial infarction**
[redacted]		BPDCN	2014-05	R/R	1	12	2015-05-11	2015-05-16	2015-05-28	13	Respiratory failure
[redacted]		AML	2015-03-09	R/R	≥4	16	2015-09-17	2015-09-19	2015-09-24	6	Acute kidney injury, Tumour lysis syndrome
[redacted]		BPDCN	2016-10	FL	0	12	2017-01-12	2017-01-13	2017-01-18	6	**Capillary leak syndrome**
[redacted]		AML	2014-01-31	R/R	3	12	2015-03-30	2015-04-22	2015-04-25	4	Sepsis, Cardiac arrest
[redacted]		AML	2013-06	R/R	≥4	16	2015-08-24	2015-08-28	2015-09-14	8	Disease progression
[redacted]		AML	2016-10-27	FL	0	12	2016-11-01	2016-11-05	2016-11-15	11	Disease progression
Study 0314											
[redacted]		MPN	--	--	--	7	2016-03-15	2016-04-08	2016-05-02	25	Cardiopulmonary failure

Pt. Number	Age/ Sex	Disease	Date of Diagnosis	Line	Prior treatment lines	Dose[1]	Treatment Start Date	Treatment End Date	Date of Death	Rel Day [1]	Cause of Death [2]
[redacted]		MPN	--	--	--	9	2016-06-21	2016-07-14	2016-07-21	8	Abdominal wall hematoma; Acute kidney injury; Hyperkaliaemia; Multiple organ dysfunction syndrome; shock haemorrhagic; Urinary tract disorder
[redacted]		MPN	--	--	--	12	2017-02-22	2017-02-24	2017-03-08	13	**Cerebrovascular accident**
[redacted]		MPN	--	--	--	12	2017-11-20	2017-11-22	2017-12-19	28	Cerebral infarction; Respiratory failure
[redacted]		MPN	--	--	--	12	2019-01-02	2019-01-04	2019-01-20	17	Intracranial haemorrhage

Abbreviations: F = female; FL = first line; M = male; MPN = myeloproliferative neoplasm; pt = patient; Rel Day = relative day; R/R = relapsed/refractory.

1. Dose in mcg/kg
2. Update on patient 09-017 was prov ded as part of the responses to the Day 90 questions.

Capillary Leak Syndrome

Capillary leak syndrome (CLS), a progressive condition characterised by a constellation of symptoms, including hypoalbuminemia, oedema, weight gain, and hypotension, that may present simultaneously or sequentially, is an adverse reaction associated with tagraxofusp and has been seen in other fusion proteins with a similar structure (McCann 2012) and with other commonly used antineoplastic agents (Jeong 2019), including gemcitabine, fludarabine and cytarabine. Therefore, treating oncologists are familiar with recognising and treating CLS.

In Stages 1-3 of study 0114, 47 BPDCN patients were treated with tagraxofusp (32 first-line [3 treated with 7 mcg/kg and 29 with 12 mcg/kg] and 15 R/R [all treated with 12 mcg/kg]):

- Overall, 9 (19%) of 47 patients with BPDCN had CLS reported as a treatment-emergent adverse event (TEAE).
- CLS was non-severe for 6 of these 9 patients, Grade 4 for 1 patient, and Grade 5 for 2 patients (1 treated with 7 mcg/kg and 1 treated with 12 mcg/kg).
- The median time to onset of CLS was short (5 days), with most patients experiencing the first onset of CLS in Cycle 1 (no patient experienced the first onset of CLS after Cycle 2).
- After presentation, the median time to resolution of CLS was 4 days, with a maximum of 19 days.
- Overall, 6 (67%) of the 9 patients with BPDCN for which CLS was reported as a TEAE were treated beyond Cycle 1, none of whom experienced recurrence of CLS on continued treatment with tagraxofusp.

In addition, 42 patients were treated in Stage 4 of the study (37 first-line and 5 R/R; all treated with 12 mcg/kg), and data on CLS in this population were similar to the data obtained from the patients treated in Stages 1-3:

- Overall, 9 (21%) of 42 patients with BPDCN had CLS reported as a TEAE.
- CLS was non-severe for 5 of these 9 patients, Grade 4 for 1 patient, and Grade 5 for 1 patient.
- The median time to onset of CLS was short (6 days), with most patients experiencing the first onset of CLS in Cycle 1 (no patient experienced the first onset of CLS after Cycle 2).

Findings for CLS among all 176 patients with haematologic malignancies treated with ≤ 12 mcg/kg of tagraxofusp as monotherapy were similar to those in patients with BPDCN:

- Overall, 32 (18%) of 176 patients had CLS reported as a TEAE.
- Most CLS events were Grade 2 in intensity (22 of 32 patients). CLS was Grade 3 and Grade 4 in intensity for 5 and 2 patients, respectively. Three cases of CLS were fatal (2%).

To date, the incidence of CLS in patients with BPDCN treated with tagraxofusp in the commercial setting (19%) was similar to the incidence in the population treated with Elzonris as monotherapy (18%), suggesting that the estimated rate of CLS in patients with BPDCN as reported in Study 0114 is an accurate estimation. Importantly most CLS cases were non-severe and resolved (69%), although 3 fatal cases occurred, all in Cycle 1 (after 2 to 5 doses of tagraxofusp). This included patient 06-007 a 64-year old male with AML who received a higher dose of tagraxofusp (16 µg/kg/day) than the to-be marketed dose. Although not definitive from the information available to the Sponsor, this patient may not have had adequate cardiac function prior to treatment start (LVEF 55%) and may have had increased weight gain that should have precluded the 3rd dose of tagraxofusp.

Management of CLS

Following the first death reported as a result of CLS, the 0114 protocol was amended (Amendment 6, 01 December 2014) to provide risk mitigation strategies for CLS including modification of the entrance criteria to require that patients have a normal LVEF before study entry and more rigorous monitoring of patients during the infusion period (planned for 5 consecutive days) in each cycle, including daily assessment of body weight. Guidance around albumin levels was provided including levels at which albumin infusions are recommended and when dosing should be held; these mitigation strategies were further refined by Amendment 7 (11 August 2015) and also were incorporated into the protocols for all other tagraxofusp studies. The incidence of ⩾Grade 3 CLS prior to implementation of these changes in the 0114 study was 17% (1/6 patients) and after implementation was 6% (7/119 patients). Furthermore, the rate of Grade 5 CLS in particular decreased from 17% (1/6) before implementation of these changes to 2% (2/119) after implementation, demonstrating the efficacy of these interventions.

Collectively, the primary manifestations of CLS appear to occur early during treatment, and generally without recurrence in subsequent cycles. Early recognition and active mitigation of these symptoms as well as temporary tagraxofusp treatment interruptions resulted in resolution of CLS in the majority of patients. Rapid reduction in serum albumin is the hallmark of CLS and is often one of the first abnormalities that present in the early stages of the syndrome. Oedema, weight gain and hypotension resulting from fluid overload are commonly observed in patients experiencing CLS. Therefore, the signs of CLS are simple to monitor in the clinic and when patients are at home.

In clinical use, implementation of these precautions will be facilitated by patients being hospitalised and closely monitored for treatment in Cycle 1.

The proposed Summary of Product Characteristics (SmPC) includes advice on reducing the risk of severe CLS and optimising the management of patients with early signs of this toxicity. These measures comprise:

- Ensuring that the patient has adequate cardiac function and a serum albumin ≥ 3.2 g/dL before initiating therapy.
- Monitoring of serum albumin levels prior to each dose of tagraxofusp and maintaining albumin levels at ≥ 3.5 g/dL with intravenous albumin supplementation as required.
- Regular assessment for other signs / symptoms of CLS including weight gain, new onset or worsening oedema, hypotension and haemodynamic instability.
- Requirement for treatment interruptions if early signs of CLS develop and until these symptoms are resolved.

Importantly, treatment interruption is a key component of the CLS risk minimisation guidelines and is recommended as part of early intervention. As previously mentioned, the proposed guidelines aim to reduce the risk of serious CLS sequelae, and not prevent or reduce the overall incidence.

The proposed patient information leaflet includes advice for patients on monitoring symptoms of CLS once they are discharged from the hospital. Per the proposed risk management plan patients will be counselled on the risk of CLS by their treating healthcare provider and will be given a patient alert card detailing the signs of CLS, what to do should they appear and who to contact.

The recommended course of treatment for CLS detailed in the proposed SmPC (administration of IV albumin and/ or methylprednisolone [or equivalent], depending on severity of symptoms) follows current clinical guidance.

The overall rate of CLS (all grades) has remained consistent between clinical trials (20% in BPDCN patients in clinical trials) and the post-marketing/EAP setting (19%), providing evidence that the

established risk mitigation measures have been effective (i.e. the incidence of CLS in the real-world setting has not increased). The applicant has implemented risk minimization activities for the European EAP, and to date, there have been no deaths due to CLS reported in the 26 patients who have received or are currently receiving treatment through the EAP.

- For the European EAP, as sites are requesting tagraxofusp for the treatment of BPDCN, the applicant is able to deliver to all sites (before tagraxofusp is delivered) an extensive training programme concerning early signs and symptoms of CLS, as well as dose modifications in case of abnormalities.

Hepatotoxicity

The exact mechanism of hepatoxicity with tagraxofusp is unknown, although it is likely to be related to a direct effect on the hepatocyte related to higher exposure to tagraxofusp in Cycle 1 of treatment and not to immune-complex formation based on the early onset of these events, noted recovery, and lack of recurrence.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased were the most common TEAEs overall.

Among the 47 patients with BPDCN treated with tagraxofusp in Stages 1-3, 31 (66%) experienced ALT increased and/or AST increased. Grade ≥3 reports of TEAEs of ALT and AST increased occurred in 17 (36%) and 16 (34%) patients, respectively. Findings were similar in the 42 patients treated in Stage 4: 28 (67%) of 42 experienced ALT increased and/or AST increased. Grade ≥3 reports of TEAEs of ALT and AST increased occurred in 11 (26%) patients each.

Overall, most patients who experienced ALT increased and AST increased did so in the first cycle. An assessment of time to first onset of increases in ALT or AST based on laboratory data (to > 3×ULN), was consistent with these results, with most increases occurring within the first treatment cycle. The incidences of liver enzymes increases in patients with BPDCN (~66%) were similar to the incidence in the population treated with Elzonris as monotherapy (~55%), suggesting that the estimated rate of hepatotoxicity in patients with BPDCN as reported in study 0114 is an accurate estimation.

Acute hepatic failure and liver encephalopathy was reported in one patient treated with Elzonris at a higher dose (16 mcg/kg). Two first-line BPDCN patients in the 0114 study met the laboratory criteria for Hy's Law, 1 based on the ALT and bilirubin criteria (Patient 02-026), and 1 based on AST and bilirubin criteria (Patient 06-001). In both patients, the LFT elevations occurred early in the patient's treatment course (Cycle 1). One of the patients (06-001) had concurrent severe CLS, which led to multiorgan failure (acute kidney injury, respiratory failure, as well as the significant elevations in LFTs) and the patient's death. The other patient continued to receive tagraxofusp following recovery of the LFT levels without further elevations reported. Both patients were receiving other confounding medications that could have led to elevations in LFTs, including acetaminophen, non-steroidal anti-inflammatory drugs, levofloxacin, and statins. Based on the Sponsor's review of these cases, neither case was considered by the Sponsor to represent drug-induced liver injury. However, information on these cases was added to the proposed SmPC.

To date, the totality of the safety data to date pertaining to hepatotoxicity support the position that drug-induced liver injury is not expected with tagraxofusp.

In terms of risk mitigation, management and monitoring, patients with severe hepatic impairment who may present an increased risk for hepatoxicity should not be treated with tagraxofusp according to the proposed SmPC which requires that serum albumin be > 3.2 g/dL.

The SmPC also advises that AST and ALT be measured before each dose and that if transaminases rise to greater than 5 times the upper limit of normal treatment should be withheld until transaminase elevations are ≤ 2.5 times the upper limit of normal.

Post-authorisation, the applicant proposes to collect data on hepatic events via a follow-up form as part of routine pharmacovigilance, as well as on hepatotoxicity via the proposed clinical PASS.

Choroid plexus lesions

Although nonclinical pharmacokinetic and toxicology studies did not assess whether tagraxofusp entered the CNS, clinical neurological findings in those studies were normal and the only notable CNS histopathological finding was that observed in the choroid.

Changes in the choroid plexus are of unknown relevance to humans. However, to monitor for this potential toxicity in the clinic, assessments for headaches and neurological signs and symptoms were required in Investigator-sponsored Study 50047 among the patients treated with Regimen A (dosing every other day for up to 6 doses). There were no clinical findings consistent with this toxicity. Consequently, this monitoring was removed from the protocol for Regimen B (daily dosing × 5) and was not employed in Stemline-sponsored studies. No findings consistent with this toxicity were seen among the 46 patients treated with Regimen B in study 50047. In the SCS pool, there was no documented evidence suggestive of choroid plexitis on neuroimaging in any of the nervous system disorder serious treatment related cases. Additionally, there were no serious nor severe adverse reactions suggestive of idiopathic raised intracranial pressures in the 141 patients included in the SCS. 3 patients in the SCS pool had Grade 5 Nervous System Disorders, including 1 patient each with AML, advanced systemic mastocytosis (ASM), and MPN. None of the patients with BPDCN had a Grade 5 Nervous System Disorder. Two of the patients received the 12 µg/kg/day dose of tagraxofusp and 1 received the 16 µg/kg/day dose. Two of the events leading to death were assessed as unrelated to study treatment (haemorrhage intracranial and cerebral infarction) and 1 (cerebrovascular accident) was assessed as treatment related by the Investigator. Based on Sponsor review of these cases there was no evidence suggesting choroid plexitis. No neurological events occurred on study 0114 in BPDCN patients that are considered related to choroid plexus deposits.

Information on the non-clinical findings are included in the proposed SmPC with full neurological examination advised if clinical signs or symptoms of CNS damage should be observed.

To further assess the mechanism of the choroid plexus findings in the non-clinical studies, the applicant will be conducting a category 3 PASS which will employ immunohistochemistry staining of brain tissue samples from non-clinical study MPI 2231 007 with the aim of determining potential toxicity biomarkers.

Conclusion

Acceptable safety has been demonstrated in a sizeable dataset (up to June 2019) of 176 patients treated with monotherapy in clinical trials and an additional 128 patients treated in the post-marketing/EAP setting. Importantly, the post-marketing/EAP experience is thus far consistent with the adverse events seen in the clinical trials, especially with regard to CLS, the incidence of which has not increased in the real-world setting, supporting the effectiveness of the risk minimisation strategies described above. The applicant has implemented risk minimization activities for the European EAP, and to date, there have been no deaths due to CLS reported in the 26 patients who have received or are currently receiving treatment through the EAP.

It is also important to note that as CLS is a known adverse reaction associated with other anti-neoplastic therapies, treating oncologists are familiar with recognising and treating CLS.

The toxicity profile is well characterized and acceptable when considered against the benefits of the drug. Uncertainties will be monitored further in the post-marketing setting, in particular through the proposed

PASS described earlier, and adequate risk minimization procedures are in place to reduce risks to patients.

Ground for refusal number 4

Therefore, taking into account these concerns in the context of a limited and heterogenous dataset, the CHMP cannot conclude that efficacy has been robustly shown. Together with the uncertainties on the safety profile, B/R cannot be established.

Ground for re-examination number 4

BPDCN is an aggressive malignancy with a short survival time. The principal goal of any therapeutic intervention in BPDCN is the achievement of a complete response, from which the relapse-free period can be extended through continued consolidation therapy with or without subsequent transplantation. There are no approved and no satisfactory treatment options for induction of remission. Combination chemotherapy regimens used in current practice are not well-documented, leading the Leukemia and Lymphoma Society 2018 to conclude "*Due to the aggressive clinical course of BPDCN and its historically poor outcome with conventional chemotherapy, referral to a clinical trial either at diagnosis or after relapse should be considered for all patients, if available*." What is well recognised is the substantial and prolonged toxicities and the risk of treatment-related death (17%-26%) associated with available chemotherapy regimens. Hence, there is a clear medical need for new therapies. Tagraxofusp is targeted treatment, developed based on the disease biology that the BPDCN malignancy arises from proliferation of malignant plasmacytoid dendritic cells (pDCs) that ubiquitously express high levels of the cell surface antigen CD123.

Study 0114 was a prospective study of tagraxofusp in patients with the same demographic and clinical characteristics as patients who present in clinical practice. The study used complete response (CR/CRc) criteria, developed in collaboration with medical experts in BPDCN (see Response to Ground 1) which are more stringent than those applied in the retrospective reviews. A complete response in an individual patient can be attributed entirely to a treatment effect of tagraxofusp because spontaneous remission of BPDCN does not occur (see Response to Ground 3). Hence, the response criteria enabled the robust demonstration of the treatment effect of tagraxofusp, with 47% (95% CI, 32.5%, 61.7%) of first-line patients in Stages 3-4 and 57% (95% CI, 44.0%, 69.2%) over Stages 1-4 achieving complete response. BPDCN is an ultra-rare disease. Nevertheless, the size of study 0114 is adequate to estimate the effects of treatment with sufficient precision to enable a benefit-risk assessment, with a lower bound of the 95% CI of 32.5% in Stages 3 and 4 and 44.0% for the pooled 4 stages of the trial. Some differences in complete response rates across trial stages were observed but, critically, a relevant magnitude of effect is established in each stage of the trial and in pooled analyses, whether including patients recruited across all trial stages or restricted to patients recruited during and after the confirmatory stage 3.

Complete response rates in elderly patients were found to be similar to those in middle-aged or younger patients. This is of note because elderly patients often do not tolerate the alternative currently available intensive chemotherapy regimens used to induce remission.

SCT is a therapeutic option for some BPDCN patients following treatment-induced disease remission. Whilst SCT use complicates an estimation of the duration of tagraxofusp-induced response, complete responses in tagraxofusp treated patients were of sufficient duration to enable one third of patients (32.3%) to bridge to SCT, extending the duration of the benefit derived from treatment. Patients who achieved CR/CRc but did not bridge to SCT also derived benefit from tagraxofusp, as evidenced by prolonged responses of >6 months and of longer duration, up to 35+ months, in 4 patients.

R/R BPDCN is known to arise by the same biological mechanism as newly diagnosed disease, involving the proliferation of malignant pDCs that ubiquitously express high levels of CD123. Consistent with the disease biology, and the targeted nature of tagraxofusp, CRs and PRs were observed in patients with R/R disease. Patients with R/R BPDCN have extremely poor prognosis and, as with all recurrent oncologic disease, become increasingly resistant over successive courses of chemotherapy. As such, tagraxofusp remains a medically relevant therapeutic option in R/R patients.

Considering the life-threatening and aggressive nature of BPDCN, tagraxofusp has demonstrated an acceptable safety profile, data is provided from 176 patients treated with monotherapy in clinical trials and an additional 128 patients treated in the post-marketing_setting in the US and an early access programme in Europe. Overall, the size of the safety database is considered appropriate to characterise the safety profile of tagraxofusp in the target population, given this is an ultra-rare disease. Of the 176 patients included in the monotherapy studies treated with tagraxofusp ≤ 12 mcg/kg, 89 were BPDCN patients treated in Stages 1-4 of study 0114. In addition to the pivotal study 0114 in BPDCN patients, safety data from 3 other applicant-sponsored studies of tagraxofusp, in haematologic malignancies other than BPDCN were included. The safety profile of tagraxofusp was largely similar in patients with haematological malignancies across the studied indications (mainly BPDCN and AML, with few patients included with diagnoses of other haematological neoplasms). These safety results show both consistency and an acceptable safety profile.

Most adverse events were transient and manageable, with few leading to treatment discontinuation, and adverse events did not accumulate over cycles of therapy. A particular benefit of tagraxofusp is that the treatment does not require prolonged hospitalization as the treatment is given as an intravenous infusion over 15 minutes, once daily, on days 1-5 of a 21-day cycle, with only the first cycle required to be administered in the in-patient setting. Furthermore, prolonged myelosuppression has not been observed with tagraxofusp.

The incidence of common TEAEs was notably lower after Cycle 2. This decrease in incidence was noted for most TEAEs. The incidences of individual TEAEs leading to discontinuation of tagraxofusp were low, indicating they were manageable. The safety profile was similar across older patients compared with middle-aged and younger patients.

Capillary leak syndrome (CLS) is the most important identified risk. It is important to note that as CLS is a known adverse reaction associated with other anti-neoplastic therapies, treating oncologists are familiar with recognising and treating it.

Findings for CLS among all 176 patients with haematologic malignancies treated with ≤ 12 mcg/kg of tagraxofusp as monotherapy were similar to those in patients with BPDCN: Overall, 32 (18%) of 176 patients had CLS reported as a TEAE. Most CLS events were Grade 2 in intensity (22 of 32 patients). CLS was Grade 3 and Grade 4 in intensity for 5 and 2 patients, respectively. Three cases of CLS were fatal (2%). To date, the incidence of CLS in patients with BPDCN treated with tagraxofusp in the commercial setting (19%) was similar to the incidence in the population treated with Elzonris as monotherapy (18%) suggesting that the rate of CLS in patients with BPDCN as reported in study 0114 is an accurate estimation. Importantly, most CLS cases were non-severe and resolved (69%), although 3 fatal cases occurred, all in Cycle 1 (after 2 to 5 doses of tagraxofusp).

Since CLS is characterized by readily recognizable symptoms and laboratory abnormalities, risk minimization guidelines were implemented in the clinical trial and are proposed in the RMP. The proposed Summary of Product Characteristics (SmPC) together with the proposed RMP duly includes advice on reducing the risk of severe CLS and optimising the management of patients with early signs of this toxicity.

Importantly, the post-marketing US/EAP in Europe experience is thus far consistent with the adverse events seen in the clinical trials, with no new safety signals identified, especially with regard to CLS. The applicant has implemented risk minimization activities for the EAP in Europe, and to date, there have been no deaths due to CLS reported in the 26 patients who have received or are currently receiving treatment through this programme.

In conclusion, the toxicity profile is well characterized and acceptable when considered against the benefits of the drug, and in the therapeutic context. The applicant recognises that uncertainties exist in all regulatory decisions, and in particular for medicines that are developed in rare diseases. The design of a PASS has been agreed to increase the extent of safety data available and to demonstrate the effectiveness of risk minimisation measures in EU clinical practice. The applicant also plans to continue to generate clinical data and increase the knowledge around the efficacy and safety of tagraxofusp in other haematologic malignancies, as monotherapy and in combination with other treatments. Should the CHMP find the benefit-risk of tagraxofusp to be positive, but would like to link approval to the generation and submission of post-authorization data, the applicant would welcome a discussion on how to refine or develop the post-authorization evidence generation.

Concluding:

- Tagraxofusp targets CD123; a rationale therapeutic target for BPDCN. Tagraxofusp induced clinically meaningful complete responses in a representative population of patients with BPDCN.
- Adverse events of tagraxofusp were typically transient and did not accumulate over cycles of therapy. Tagraxofusp is not associated with prolonged myelosuppression. Risk minimisation strategies for CLS are proving effective based on, on-market experience in US as well patients treated within the EU EAP.
- The benefit of inducing CR/CRc in over 50% of treated patients and enabling SCT in 32% of patients outweigh the adverse event profile, in particular considering the current absence of satisfactory treatment options.

Thus, the benefit-risk of tagraxofusp in BPDCN is positive.

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant’s response.

Report from the SAG

The SAG is expected to comment on the CHMP grounds for refusal:

In the context of a one-pivotal-trial scenario, the evidence in support of the claimed indication of tagraxofusp as monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) is considered insufficient:

- The pivotal 4 cohort phase I/II study has important limitations rendering the benefit of tagraxofusp not robustly demonstrated in the context of a single pivotal trial with a non-randomised design and a small sample size. A total of 84 BPDCN patients (n=65 first line and n=19 second line) have been enrolled.
- Statistical analysis was only planned for cohort 3 of the study in which a total of 13 first line patients were enrolled. Study 0114 was thus not designed to detect a particular magnitude of effect in the BPDCN population as studied.

- Pivotal efficacy results showed an anti-disease activity in cohort 3 with a complete response rate (CR/CRc) of 53.8%. However:

i) The magnitude of the efficacy response was highly heterogeneous across the 4 stages;

ii) It is not clear why CR rate and HSCT decreased over time in the successive cohorts;

iii) The activity seen in second line are unlikely to represent benefit for the second line population;

iv) The safety profile is not well characterized.

- Therefore, taking into account these concerns in the context of a limited and heterogenous dataset, the CHMP cannot conclude that efficacy has been robustly shown. Together with the uncertainties on the safety profile, B/R cannot be established.

The SAG discussed the therapeutic context of treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). The SAG agreed that this is a very challenging clinical and research setting due to the rarity of the disease (even larger centres would see only 1-2 patients a year), the highly aggressive natural history of this multi-organ systemic disease (8 to 14 months in first-line setting with standard chemotherapy regimens also in patients with "skin-only" disease), and the high incidence in elderly patients that often cannot tolerate induction chemotherapy followed by stem cell transplantation. Currently, there is no agreement as to what type of chemotherapy should be used in these patients. Among the SAG experts, some prefer AML-type regimens, while others ALL or NHL-type type regimens without sufficient long-lasting remissions except in selected patients achieving allogeneic stem cell transplantation (ASCT). There is no prospective comparison or even assessment of these regimens. Also that none of these chemotherapy regimens has ever been assessed prospectively. In this high unmet need situation, prospective evaluation of current practices and of further active treatments are urgently needed.

Tagraxofusp is a targeted agent against CD123 that is highly expressed in BPDCN. Thus, there is a sound biological rational for tagraxofusp in this disease and this is supported by available in vitro and in vivo studies.

The SAG discussed in detail the available evidence and considerations presented by the rapporteurs and the applicant. In general, the SAG agreed that efficacy has been demonstrated on the basis of complete response (CR), successful achievement of allogeneic stem-cell transplantation (ASCT), and durable remissions. The ability of patients to achieve CR, a prerequisite for ASCT, is remarkable considering that ASCT was not considered suitable for patients entering the trial. Allowing patients to proceed to ASCT, which is the only option with curative potential and long-lasting remissions, is a clear clinical benefit in this high unmet need situation. Some SAG members also highlighted that relapse is relatively common even after ASCT, which was not the case, apparently, in this trial.

The SAG agreed that precise efficacy data are not available, and that patient selection may have led to overestimate the true effect on CR. The heterogeneity observed in the various cohorts of the trial determines a rather wide uncertainty around the true estimate. However, the existence of an important effect associated with tagraxofusp in terms of patients achieving CRs, undergoing successful ASCT, and achieving long-term remissions, is clearly shown taking into account the predictable natural history of the disease and the range of effects that have been described in small retrospective series with intensive chemotherapy treatment options that are considered standard in this setting. The SAG was in agreement that clinically relevant efficacy has been demonstrated. There are not enough data to demonstrate its curative potential as monotherapy or duration of response and survival in patients who did not undergo ASCT after having achieved a CR. However, tagraxofusp may be potentially curative for some patients which are consolidated with ASCT.

Although there was general agreement that a clinical benefit has been established some members regretted that lack of a randomized controlled trial did not allow a robust comparison to available intensive chemotherapy regimens. However, the majority of SAG members considered that RCTs, although theoretically possible, would have been extremely challenging due to the rarity of the disease and acknowledged that study 0114 is the only prospective trial with pre-specified response criteria performed in this rare disease. Some SAG members noted that in the post marketing setting, more than 120 patients have been treated with tagraxofusp within a rather short time suggesting that a small randomized trial vs. physician's choice would have been possible despite the rarity of this disease. Others, however, noted that many centres would have to be opened to achieve even a small sample size and that this is not realistic given that most centres will not open a clinical trial when they expect to include only 1-2 patients/year. Nevertheless, the SAG agreed that it would be important to generate more efficacy and safety data to refine the understanding of benefits and harms in a broader population to optimise patient selection and treatment decisions.

It was also noted that the definition of CR in the trial was unusual, since it required the conventional normalization of peripheral blood, bone marrow, and lymphadenopathy but allowed for "residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)". Although a skin biopsy showing residual tumour cells may not be critical in the decision of undergoing ASCT, assessment of the success of this procedure depending on microscopic residual skin disease could be further explored.

The SAG also agreed that toxicity was clinically significant but manageable and that there is a high unmet need for less toxic options compared to intensive chemotherapy. Based on the available data, the overall toxicity profile tagraxofusp compares favourably to available options. The better safety profile associated with tagraxofusp may be important also in ensuring that patients can successfully undergo ASCT.

Although some SAG members expressed some concerns about the high incidence of capillary leak syndrome (CLS) and 11% deaths that occurred within 30 days of last tagraxofusp dose in the clinical studies (n=21/190 all dose, monotherapy; see rapporteur report) even in experienced haematological centres, in general, the safety profile compared to intensive chemotherapy was considered a major advantage compared to the most active available treatments.

In conclusion, notwithstanding all the methodological weaknesses, potential selection bias, and need for a more precise understanding of benefits and harms in a wider population, the SAG agreed that benefit has been established and that the toxicity profile is acceptable.

From a clinical perspective this additional therapeutic option is welcome in this very rare disease and high unmet need situation. The SAG agreed that it is important to manage the toxicity using adequate risk minimisation measures and to acknowledge uncertainties on the precise benefits associated with tagraxofusp until more precise data become available. Many other clinical questions remain open and hence the need for optimising treatment post-approval. For instance, according to some experts, tagraxofusp could become an important treatment for younger and fitter patients to minimise the risks of hampering ASCT with the toxicity associated with intensive chemotherapy (neutropenia, sepsis, etc.) Others thought that intensive chemotherapy should be the preferred option in fit patients and this treatment may be more interesting for elderly and frail patients, to avoid the toxicity of intensive chemotherapy that should be the preferred options in fit patients, although the data in the pivotal study were more representative of a fit population (ECOG PS mainly 0-1). Lastly, risk factors for capillary leak syndrome and other severe toxicity should be studied further. Clearly, more data will be needed to better define the treatments of choice in this disease.

Concerning the grounds for refusal,

- The SAG did not support the conclusion that the evidence is considered insufficient to support the claimed indication, except perhaps in the second-line setting especially taken the toxicity into consideration. Only very few patients in the study received tagraxofusp as second-line treatment and only very short response durations were observed. These aspects should be carefully considered if extrapolation from first-line is attempted, although the SAG acknowledged that it is extremely challenging to conduct separate studies in this even rarer and higher unmet need population.
- The known methodological limitations associated with single-arm trials, pooling of cohorts within exploratory trials, and heterogeneity observed in the different cohorts and over time, do not per se invalidate the clinical benefit observed in many patients. It is important to remember that available therapeutic options also have huge uncertainties and heterogeneity observed across series (with no general agreement regarding which is the best treatment for this condition). The basis of evidence is considered limited but not unusual or insufficient in these settings when the effect of the drug is clear and there are no alternatives proven to be associated with a clearly better efficacy or safety profile, or fewer uncertainties.
- The SAG considered that the beneficial effect observed in some patients is clinically relevant and can be attributed to tagraxofusp (despite remaining uncertainties about the precise magnitude of effect in a broader population).
- The SAG considered that the safety profile is sufficiently well characterised to allow informed clinical decisions and an assessment of the balance of benefits and harms in the clinical setting.

  Furthermore, the SAG agreed that the toxicity profile was undoubtedly more favourable compared to that associated with standard intensive chemotherapy. This also could be relevant for elderly and frail patients due to poor tolerability, or when, due to toxicity, there may be a risk of hampering subsequent ASCT.

  Post-authorisation data should be collected to optimise the understanding of efficacy and safety in a broader population.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

The CHMP considered that blastic plasmacytoid dendritic cell neoplasm (BPDCN), is a rare haematological disorder with approximately 700 and 1000 incident cases annually in the US and Europe, respectively. The prognosis is poor, with median duration of overall survival after diagnosis reported at 9-13 months unless patients can undergo allogeneic stem cell transplantation (SCT), associated with median duration of overall survival of 30 months or longer.

Eligibility for SCT requires induction treatment to achieve a complete response (CR), a prerequisite for a successful procedure. There are no medicines specifically authorised for the treatment of BPDCN. However, a variety of approaches are currently used successfully to treat patients with treatment-naïve BPDCN using acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), or non-Hodgkin lymphoma (NHL)-like intensive chemotherapy regimens, with the aim of inducing CR to allow subsequent ASCT. The efficacy of these therapies is ill-documented (including the lack of a standard definition of CR). CR rates in the range of 10% to 60% have been observed using variable regimens in small retrospective series. Such regimens are associated with high toxicity including treatment-related mortality in the range of 17% to 26%.

The pivotal study 0114 was the first prospective clinical trial in BPDCN. This was a multi cohort single-arm trial (SAT) conducted over 6 years. The primary outcome was considered relevant to capture clinical benefit insofar as it allowed bridging to SCT. Although a randomized comparison of efficacy and safety to currently used regimen would have been useful to contextualise the effects, the effects on CR observed in the single-arm trial can be convincingly attributed to tagraxofusp as spontaneous remissions can be excluded based on the known natural history of the disease. Furthermore, the observed results in terms of successful SCT and long survival in some patients confirm the favourable effect of the CRs associated with tagraxofusp. Some heterogeneity of CR and the proportion of patients undergoing successful SCT across the respective "stages" of the pivotal trial can be expected given the small size of the trial.

Considering also the SAG advice on the clinical relevance of the observed results and the challenges of conducting randomized controlled trials in this rare population, the CHMP concluded that efficacy has been demonstrated in first-line treatment of BPDCN. However, the dataset in the treatment of relapsed or refractory (2^{nd}-line) BPDCN is too small to draw any conclusions.

Safety results of tagraxofusp in BPDCN population are mainly coming from the study STML-401-0114 (study 0114); additional safety data also included data from studies 0214 (for adverse risk AML), 0314 (for advanced high-risk myeloproliferative neoplasms) and 0414 (for relapsed or refractory multiple myeloma), using a variety of doses. The safety profile of tagrasofusp is non-trivial, including hepatotoxicity and potentially lethal capillary leak syndrome. However, the overall treatment-associated mortality is not higher than what has been reported with intensive chemotherapy. The proposed SmPC provides risk mitigation advice for the key toxicities. The educational programme for the healthcare professionals to enhance the awareness of the early signs and symptoms of capillary leak syndrome (CLS) together with the patient card were considered adequate to minimise this risk. Also considering the SAG advice, the CHMP concluded that the safety profile was considered manageable and acceptable in this therapeutic context.

Therefore, based on the totality of the data, the grounds for re-examination and the advice from the SAG, the CHMP concluded that:

- The efficacy demonstrated in a small SAT in this rare, aggressive disorder with no approved treatment alternatives, is considered relevant. The side effect profile is non-trivial but acceptable in the context.
- The benefits in previously untreated patients outweigh the risks. Benefit in the relapsed or refractory setting has not been established and the indication should therefore be restricted to 1^{st}-line treatment only.

Due to the lack of a randomised control group, drug effects on overall survival cannot be isolated. Furthermore, patient selection may result in over-estimation of the treatment effect. Lastly, refining the understanding of benefits and harms based on patient, treatment and disease characteristics is not possible in such small populations. Given the challenges of conducting randomized controlled trials in this disease and the many available treatment options, direct comparisons are difficult to obtain, comprehensive data are not anticipated to be generated and some considerable level of uncertainty is likely to persist on these aspects.

The applicant agreed to the proposed indication.

The CHMP agreed that the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication is too rare. Therefore, the CHMP recommended that a marketing authorisation under "exceptional circumstances" be granted due to the rarity of the disease. In this context, the applicant is required to submit the results from an

observational study (e.g., using a registry) of sufficient size and duration to study these aspects, including planned comparative matched analyses using relevant external controls.

5.1. Risk Management Plan

The CHMP endorsed RMP version 1.5 with the following content:

Safety concerns

Summary table of the safety concerns:

Summary of Safety Concerns	
Important identified risks	Capillary Leak Syndrome
Important potential risks	Hepatotoxicity Choroid Plexus Lesions
Missing information	Use in patients with severe renal impairment Use in hepatic impairment Use in patients with significant cardiovascular history Drug interaction data

Pharmacovigilance plan

Summary table of additional Pharmacovigilance activities:

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3- Required additional pharmacovigilance activities				
Immunohistochemistry staining of brain tissue samples from non-clinical Study MPI 2231 007 Planned	Determine potential toxicity biomarker(s)	Important potential risk of 'Choroid plexus lesions'	Final report	Within 6 months of EC decision

Risk minimisation measures

Summary table of risk minimisation measures:

Safety concern	Risk minimisation measures
Identified risks	
Capillary Leak Syndrome	Routine risk minimisation measures: SmPC Section 4.2, 4.4 and 4.8 PIL sections 2 and 4 SmPC section 4.4 where advice is given on management of CLS Additional risk minimisation measures: Healthcare Professional Guide Patient Alert Card
Potential risks	
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.4 4.8 PIL section 4
Choroid Plexus Lesions	Routine risk minimisation measures: SmPC Section 4.4 PIL section 4
Missing Information	
Use in patients with hepatic impairment	Routine risk minimisation measures: SmPC section 5.2
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC section 4.2 and 5.2
Use in patients with significant cardiovascular history	Routine risk minimisation measures: SmPC section 4.2 and 4.4

Safety concern	Risk minimisation measures
Drug interaction data	Routine risk minimisation measures: SmPC section 4.5

6.1. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21 December 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

6.2. Product information

6.2.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

6.2.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Elzonris (tagraxofusp) is included in the additional monitoring list as

- It is a biological product that is not covered by the previous category and authorised after 1 January 2011.
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

7. Benefit-risk balance following re-examination

7.1. Therapeutic Context

7.1.1. Disease or condition

Prevalence

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), is a rare haematological disorder derived from the precursor of plasmacytoid dendritic cells currently categorized under acute myeloid leukaemia and related precursor neoplasms in the 2008 WHO classification.

The prevalence estimate for BPDCN, in line with the information presented for the EU orphan designation application, is 1.2 per 10,000. BPDCN may constitute approximately 0.44% of haematologic cancers annually, or approximately 700 and 1000 incident cases annually in the US and Europe, respectively.

Prognosis and management

The disease has a proclivity to involve the skin, bone marrow, and lymph nodes. Prognosis is miserable unless patients can be bridged to stem cell transplantation (SCT), with median OS after diagnosis reported at 9-13 months. Bridging to SCT involves treating patients with combination chemotherapy to induce a complete response (CR) prior to the procedure.

7.1.2. Available therapies and unmet medical need

There are no medicines specifically authorised for the treatment of BPDCN and no standard of care treatment has been established for patients with newly diagnosed (first-line) or previously treated (relapsed/refractory) disease.

Therapies historically employed to treat patients with treatment-naïve BPDCN include versions of those, used for aggressive haematologic malignancies, including CHOP or CHOP-like; cytarabine plus an anthracycline; or hyper-CVAD alternating with methotrexate, and cytarabine.

The efficacy of these therapies is ill-documented (including the lack of a standard definition of CR). Furthermore, they exhibit substantial toxicity, with treatment associated mortality of 17-26% reported in retrospective case series (Pagano et al 2013; Martin-Martin et al 2015).

Thus, there is an unmet medical need in BPDCN.

7.1.3. Main clinical studies

7.2. Favourable effects

The pivotal study 0114 was the first prospective clinical trial in BPDCN. This was a multi cohort single-arm trial (SAT) conducted over 6 years. Cohorts or "stage" 1,2 and 4 included both previously untreated as well as relapsed/refractory patients with BPDCN and other haematological malignancies, namely acute myeloid leukaemia (AML). Cohort 3 was identified as pivotal by the applicant. It recruited only patients with first-line BPDCN. Its objective was to evaluate efficacy and safety supporting the indication for the treatment of adult patients with first-line BPDCN.

The sample size for stage 3 was calculated to provide at least 90% power at a two-sided Type I error rate of 0.05 to reject a null hypothesis that the rate of complete response (CR+CRc) was ≤ 10%, if the true rate was 60%. This success criterion was not agreed with EU regulators. The study 0114 was not sized to detect a particular magnitude of an effect for R/R BPDCN population.

CR is defined as complete resolution of the disease. CRc is defined similarly but allows for residual hyperpigmentation or histological abnormality in the skin. Neither CR nor CRc is anticipated to occur spontaneously in the absence of therapy. Therefore, the SAT design is sufficient to isolate drug effects.

The primary outcome is considered to capture clinical benefit insofar as it allows bridging to SCT.

A total of 84 patients with BPDCN (65 first-line and 19 R/R) were treated with 12 mg/kg and evaluated for efficacy in the 4 stages of Study 0114. At study entry, none of the patients with BPDCN were considered eligible for immediate SCT because they had active disease and were therefore in need of a treatment that could potentially induce complete remission prior to being considered for SCT-conditioning.

Complete Response for the pivotal Stage 3 (N=13) was CR/CRc = 7 (53.8%), [95% CI (25.1, 80.8)].

The overall CR rate (n=65) was 57%; 95% CI (44-69). The overall rate of bridging to SCT was 32%; 95% CI (21-45).

Duration of response was fundamentally a function of whether patients were bridged to SCT or not. 44.8% (13/29) patients were bridged to SCT with 10 patients of 13 (77%) alive and still in response as of the updated time-to event analysis. In patients not bridged to SCT (n=9+9) median DoR was 3.7 months in stages 1-3 and 2.7 months in stage 4. Similarly, OS was mainly a function of bridging to SCT.

In patients with R/R BPDCN, the CR rate was 3/19. One patient was bridged to SCT.

7.3. Uncertainties and limitations about favourable effects

Due to the nature of the pivotal study (SAT), and the absence of a randomised control group, drug effects on OS cannot be isolated.

Since the success criteria of the prospective hypothesis test designed for the Stage 3 cohort cannot be agreed with regard to clinical relevance, the pivotal study is essentially viewed as an extended case series. The variable outcomes between the different subcohorts makes the precise effect estimate uncertain.

Except for the primary endpoint in Stage 3, the applicant has not defined endpoints in the different subgroups including the R/R population. The dataset in the R/R BPDCN is so small that the drug effect cannot be reliably quantified.

7.4. Unfavourable effects

The total size of the safety dataset assessed by the CHMP in the original MAA evaluation, is given as 239 patients. Safety results of tagraxofusp in BPDCN population are mainly coming from the study STML-401-0114 (study 0114). However, the Summary of Clinical Safety (SCS) pool also included data from studies 0214 (for adverse risk AML), 0314 (for advanced high-risk myeloproliferative neoplasms) and 0414 (for R/R multiple myeloma).

113 patients received tagraxofusp at the intended dose (12 mcg/kg). Overall, 96 patients were enrolled in the study 0114; 47 BPDCN (32 first line and 15 R/R) and 49 AML patients. From these

BPDCN patients, 3 first line BPDCN patients received tagraxofusp at 7 µg/kg/day, 29 first line BPDCN patients received tagraxofusp at 12 µg/kg/day, and 15 R/R BPDCN patients received tagraxofusp at 12 µg/kg/day.

According to data provided from study 0114, median duration of exposure to tagraxofusp was 96 days (approximately 3.2 months) and 48 days (approximately 1.6 months) for first-line and R/R BPDCN, respectively. The median number of started cycles were 5.0 cycles and 3.0 cycles for first-line and R/R BPDCN, respectively.

TEAE leading to treatment discontinuation was reported in 2% (1/47). Overall, 68.1% of all the BPDCN patients reported any TEAE leading to dose interruption and 2.1% reported any TEAE leading to dose reduction.

The most common TEAE regardless of grade were ALT increased (63.8%), AST increased (59.6%), hypoalbuminaemia (55.3%), oedema peripheral (51.1%) and thrombocytopenia (48.9%), fatigue (44.7%), pyrexia (44.7%), nausea (46.8%), weight increased (38.3%), hyperglycaemia (36.2%), chills (34.0%), hypotension (27.7%), headache (25.5%), decrease appetite (25.5%), back pain (25.5%), anaemia (23.4%), constipation (23.4%), hypocalcaemia (23.4%), hypokalaemia (21.3%) and hypertension (21.3%).

Grade ≥3 TEAEs were reported at least once for 80.9% (38/47) of the total of the BPDCN patients. The most common ≥Grade 3 TEAEs reported were thrombocytopenia (31.2%), ALT increased (24.8%), AST increased (24.1%) and anaemia (19.9%). Results were similar for the patients of the SCS pool.

SAEs were reported at least once in 48.9% (23/47) of the BPDCN patients. The most common reported TESAEs were Capillary leak syndrome (8.5%), pyrexia (6.4%), AST increased (4.3%) and hypertension (4.3%).

TEAEs leading to death were reported in 6.4% of patients.

Within the safety reporting period of 30 days after the last dose of tagraxofusp in the applicant-sponsored studies, 11% of patients died.

The most significant AESI is capillary leak syndrome (CLS). Findings for CLS among all 176 patients with haematologic malignancies treated with ≤ 12 mcg/kg of tagraxofusp as monotherapy were similar to those in patients with BPDCN:

Overall, 32 (18%) of 176 patients had CLS reported as a TEAE. Most CLS events were Grade 2 in intensity (22 of 32 patients). CLS was Grade 3 and Grade 4 in intensity for 5 and 2 patients, respectively. Three cases of CLS were fatal (2%).

The proposed Summary of Product Characteristics (SmPC) includes advice on reducing the risk of severe CLS and optimising the management of patients with early signs of this toxicity. The educational programme for the healthcare professionals to enhance the awareness of the early signs and symptoms of capillary leak syndrome (CLS) together with the patient card are considered adequate to minimise this risk.

7.5. Uncertainties and limitations about unfavourable effects

All safety data come from SAT's. Therefore, drug effects cannot be reliably isolated, unless the adverse effect in question may be anticipated not to occur in the absence of therapy.

The safety database is small; therefore, frequency estimates are uncertain.

7.6. Effects Table

Table 102. Effects Table for tagraxofusp in all patients with first-line BPCDN.

Effect	Short Description	Unit	Tagraxofusp	Control	Uncertainties/ Strength of evidence
Favourable Effects					
CR/CRc* Rate	Includes all stages	N (%) (95% CI)	21 (72.4) (52.8, 87.3)	N/A	Due to small sample size, the estimate is imprecise
Median Duration of CR/CRc	Includes all stages	months	Not Reached	N/A	
Bridge to Stem Cell Transplant Rate	Includes all stages	N (%)	13 (44.8)	N/A	
Unfavourable Effects					
TEAEs	regardless causality	%	100	N/A	
TEAEs Grade ≥ 3	regardless causality	%	80.9	N/A	
Serious AEs	regardless causality	%	48.9	N/A	
TEAEs leading to discontinuation	regardless causality	%	2.1	N/A	
TEAEs leading to reduction	regardless causality	%	2.1	N/A	
TEAEs leading to interruption	regardless causality	%	68.1	N/A	
TEAEs leading to death	regardless causality	%	6.4	N/A	
CLS		%	17%	N/A	

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

BPDCN is an ultra-rare, highly aggressive haematological malignancy. OS is short, and the only way to provide durable clinical benefit is through SCT. There are no approved drugs for this condition. The treatment strategy is to use empirical combination chemotherapy to induce CR and thereby bridge to SCT. The level of documentation for the efficacy and safety of this approach is very poor. There is an unmet medical need.

The applicant has provided data from a single arm trial of 69 previously untreated patients and 20 patients in the relapsed/refractory setting, in this very rare disorder. Since CR does not occur without therapy, this study isolates drug effects on a clinically relevant endpoint. Thus, the antitumoral activity of tagraxofusp is established.

The hypothesis test embedded in the trial is not considered relevant with respect to establishing the clinical relevance of findings. A further concern is the heterogeneity of CR/CRd and the proportion bridged to SCT in the respective "stages" or subcohorts of the pivotal trial. Given the sample size, however, heterogeneity in point estimates is anticipated. Also if true activity is in line with the estimates from the worst-performing stage 4 (44% CR, 22% bridged to SCT), it would be considered established that tagraxofusp provides clinical benefit by allowing bridging to SCT in a non-negligible portion of patients.

The DoR was sufficient to allow for bridging to transplant in about one third of the patients. However, its median duration in the absence of SCT was less than six months. Therefore, the most evident established benefit of tagraxofusp is its ability to provide bridging to SCT.

The safety profile of tagraxofusp is non-trivial, including hepatotoxicity and potentially lethal capillary leak syndrome. However, the overall treatment-associated mortality is not higher than what has been reported with empirical chemotherapy, and importantly its haematological toxicity is limited. The proposed SmPC provides risk mitigation advice for the principal toxicities.

The efficacy of tagraxofusp has been demonstrated in previously untreated patients. Data in the R/R setting does not independently allow for such an inference.

7.7.2. Balance of benefits and risks

The efficacy demonstrated in a small SAT in this rare, aggressive disorder with no approved treatment alternatives, is considered relevant. The side effect profile is non-trivial but acceptable in the context. The benefits in previously untreated patients outweigh the risks. Benefits in the R/R setting have not been established as the pivotal study 0114 was not designed to formally test statistical hypothesis and its clinical relevance in this population.

7.7.3. Additional considerations on the benefit-risk balance

As is evident from the above, there is an unmet medical need in this rare disorder with no approved treatment options. The B/R of tagraxofusp is positive in previously untreated (first-line) patients. However, due to the size of the database for safety as well as efficacy, and consequent uncertainties, data cannot be deemed comprehensive. Furthermore, due to the rarity of the disease, comprehensive data are not anticipated to be generated. Therefore, an approval based on exceptional circumstances is relevant.

In this context, the applicant is required to submit the results from an observational study (e.g., using a registry) of sufficient size and duration to study these aspects, including planned comparative matched analyses using relevant external controls.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the re-examination, after having consulted the applicant.

The CHMP considered that blastic plasmacytoid dendritic cell neoplasm (BPDCN), is a rare haematological disorder with approximately 700 and 1000 incident cases annually in the US and Europe, respectively. The prognosis is poor, with median duration of overall survival after diagnosis reported at 9-13 months unless patients can undergo allogeneic stem cell transplantation (SCT),

associated with median duration of overall survival of 30 months or longer. The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indication applied for is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. In this context, the applicant is required to submit the results from an observational study (e.g., using a registry) of sufficient size and duration to study these aspects, including planned comparative matched analyses using relevant external controls.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

7.8. Conclusions

The overall B/R of Elzonris is positive provided the conditions outlined in the recommendations are fulfilled.

8. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the benefit-risk balance of Elzonris in the following indication:

Elzonris is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (see section 5.1).

is favourable. The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent

updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Elzonris in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at healthcare professionals to enhance their awareness of the early signs and symptoms of specific adverse reactions associated with capillary leak syndrome (CLS).

The MAH shall ensure that in each Member State where Elzonris is marketed, all healthcare professionals who are expected to use Elzonris are provided with the following educational package:

- Guide for healthcare professionals
- Patient alert card

- **Guide for healthcare professionals**:
  - Description of CLS which can occur with Elzonris
  - Before initiating Elzonris therapy check cardiac function and serum albumin
  - During treatment monitor serum albumin, weight gain, new onset or worsening oedema, including pulmonary oedema and hypotension including haemodynamic instability
  - Inform the patient about the risk of CLS and how to recognise CLS symptoms
  - Provide patients with the patient alert card
- **Patient alert card:**
  - That Elzonris treatment may increase the potential risk of CLS
  - Signs or symptoms of CLS
  - Patients experiencing or suspecting CLS should immediately contact their prescriber
  - Contact details of the Elzonris prescriber

Specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to collect further safety and efficacy data for Elzonris, the MAH should submit the results of a study based on a registry in patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) according to an agreed protocol.	Reports to be submitted as part of the annual re-assessment

New Active Substance Status

In light of the re-examination opinion, CHMP considers that tagraxofusp is a new active substance. The applicant has demonstrated that it is chemically distinct and neither it, nor its derivatives and salts, have ever been active substances in products authorised in the EEA.

9. Appendix

1. Divergent position to the majority recommendation for the initial opinion:

DIVERGENT POSITION DATED 23 July 2020

Elzonris EMEA/H/C/005031/0000

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Elzonris indicated as monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

The reason for divergent opinion was the following:

BPDCN is an ultra-rare malignancy with a short survival time, where bridging to stem cell transplantation is the only way to induce longer term remission. There are no approved therapies, whereas those that are used in clinical practice, are poorly documented. It has been shown that tagraxofusp has clinically relevant activity and can be used to bridge patients to SCT. The toxicity profile is non-trivial, but in accordance with the SAG opinion, this is deemed manageable given risk mitigation strategies, and acceptable in the therapeutic context. In summary, B/R has been shown to be positive, though the precise wording of the indication would remain to be specified.

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