25 January 2024
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Oncaspar

Pegaspargase

Procedure no: EMEA/H/C/003789/P46/008

Note

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

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1. Introduction

On the 13th of july 2023, the MAH submitted a completed paediatric study (CL2-095014-003 study) for Pegaspargase (oncaspar), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Steps taken for the assessment	
Description	**Date**
Start of procedure	14 Aug 2023
CHMP Rapporteur Assessment Report	19 Sept 2023
CHMP members comments	02 Oct 2023
Updated CHMP Rapporteur Assessment Report	05 Oct 2023
CHMP adoption of conclusions:	12 Oct 2023
Submission of responses	13 Dec 2023
Re-start of procedure	27 Dec 2023
CHMP Rapporteur Assessment Report	03 Jan 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
CHMP adoption of conclusions:	25 Jan 2024

2. Scientific discussion

2.1. Information on the development program and the pharmaceutical formulation used in the study

Pegaspargase is a pegylated formulation of native L-asparaginase with polyethylene glycol (PEG). In this document pegaspargase is also called S095014 (Servier code). The use of pegaspargase in the treatment of Acute Lymphoblastic Leukaemia (ALL) is very well established in clinical practice and this product is currently approved (under the trade name Oncaspar®) in 73 countries.

The initial marketing authorisation approvals were with the liquid presentation (*i.e.* USA in 01/02/1994). On 14 January 2016, pegaspargase solution received approval as a component of antineoplastic combination therapy in paediatric and adult patients with ALL via the centralised procedure in the European Union (EU).

The lyophilised powder formulation of Oncaspar®, was approved in the EU on 08 December 2017. Consequently, the Applicant decided to discontinue the liquid pegaspargase presentation; this pharmaceutical form is no longer marketed, and the deletion was approved on 02 June 2022. The estimated cumulative exposure to Oncaspar® since the first Marketing Authorisation (MA) 01/02/1994 to 14/01/2023 is at 193 544 patients.

The previously reported phase 2 clinical study, CL2-095014-002, compared the PK of the lyophilized formulation of Oncaspar® to liquid formulation during the induction phase (approximately 30 days) in newly diagnosed paediatric patients with ALL.

The present study, CL2-095014-003, was designed as a roll-over study to provide continued access to lyophilized formulation of Oncaspar® for patients who were clinically benefitting from the study drug without major toxicity and wished to continue this treatment in the following consolidation phase.

The IV infusions of Oncaspar® were given in combination with other backbone chemotherapy agents as per the ALL-MB 2015 protocol.

The CL2-095014-003 study falls into the scope of article 46 of Regulation (EC) No 1901/2006 as this is a Paediatric Study Sponsored by Servier. This study was conducted in Russia, where lyophilized formulation of Oncaspar® was approved on 04 February 2022.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for CL2-095014-003 study. CL2-095014-003 is a multicentre, open-label, roll-over study from the previously completed CL2-095014-002 study. It was designed to provide continued access to lyophilized formulation of pegaspargase (S095014) during the consolidation phase in patients who were clinically benefitting from pegaspargase (from the CL2-095014-002 study) and without major toxicity following the induction phase. No efficacy or PK endpoints were assessed.

2.2.2. Clinical study

CL2-095014-003 study

Description

A multicenter, roll-over study to provide continued treatment with lyophilized pegaspargase (S95014) in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL).

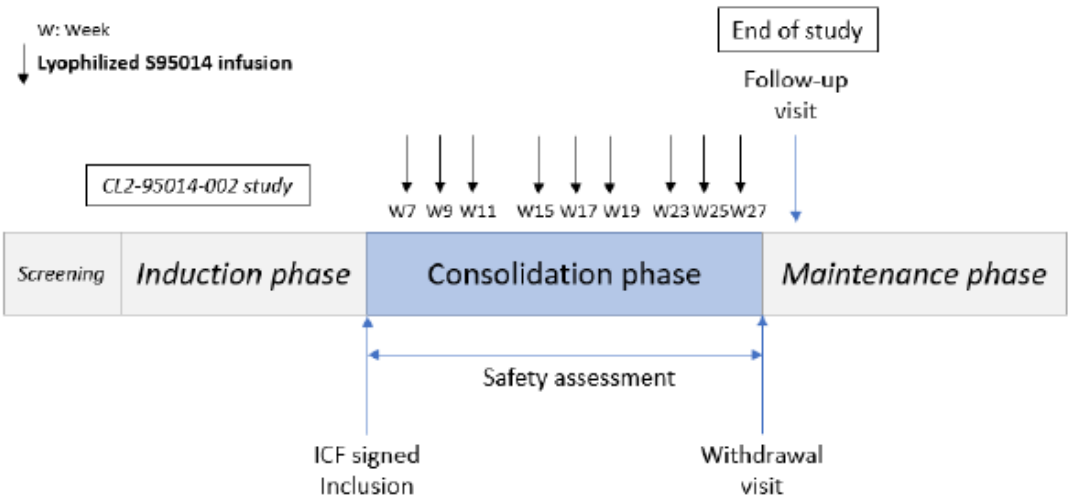
Methods

The safety assessments (laboratory tests, ECG, cardiac imaging) and pregnancy tests performed during the withdrawal visit of the initial CL2-95014-002 study were used to assess the eligibility for this roll-over study.
75 informed consents were signed; 74 patients were treated and analyzed.

The study planned to enroll 75 patients. Overall 74 patients were treated and analyzed. The study duration was approximately 7 months, including the treatment and follow-up periods.

The study plan is shown in (Figure (3.4.2) 1). The study duration was approximately 7 months, including the treatment and follow-up periods. Pegaspargase was administered every two weeks during the consolidation phase for a total of 9 infusions, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27. The investigators had the choice of administering a dose of 1000, 2000 or 2500 U/m².Patients also received other backbone chemotherapy agents as per the ALL-MB 2015 protocol. After completing the consolidation phase, patients were discontinued from the study and treated as per investigator's judgment.

Figure (3.4.2) 1 - Study design - CL2-095014-003



The inclusion visit of CL2-095014-003 study corresponded to the withdrawal visit of the initial CL2-095014-002 study.
A withdrawal visit was performed no later than 30 days after the last dose of pegaspargase during the consolidation phase. Patients then continued to receive the backbone chemotherapeutic regimen as per ALL MB 2015 protocol, and according to the physician's judgment. A follow-up visit (either direct contact or by telephone) was carried out not earlier than 30 days after the last infusion of pegaspargase, except in case of consent withdrawal. Any follow-up of adverse events and the patient survival was recorded.

Objective(s)

The study was initiated on the May 15th, 2021 and completed on January 23rd, 2023.

The primary objective of the study was:

To provide continued access to lyophilized pegaspargase during the consolidation phase.

A secondary objective was:

To assess the safety profile of pegaspargase during the consolidation phase. The study was initiated on the May 15th, 2021 and completed on January 23rd, 2023.

Endpoints

Efficacy assessment:

None

Safety assessments:

- Adverse events (AEs), treatment emergent AEs (TEAEs).
- Physical examinations and ECOG PS.
- Laboratory abnormalities assessment including hematology, blood biochemistry, urinalysis, and coagulation parameters.
- Vital signs.

Assessor's comments

This roll-over study design included paediatric population with newly diagnosed, untreated acute lymphoblastic leukemia (ALL) who had completed the CL2-95014-002 study and who were clinically benefitting from S95014 without major toxicity. 74 patients out of 89 patients included in the CL1-95014-002 study continued in this roll-over study. The study indication and population are in line with the EU marketing authorisation of oncaspar.

No statistical analysis were performed in this study and the focus was only on safety endpoints. This study design is appropriate.

Clinical Results

Disposition of subjects

A total of 74 patients were treated and analysed in the study. Of these, 22 (29.7%) were prematurely withdrawn (Table (3.4.3.1) 1): 18 due to an adverse event and 4 due to the physician's decision. All analyses were performed on the Safety Analysis Set (SAS).

Table (3.4.3.1) 1 - Subject Disposition - Safety Analysis Set - CL2-095014-003

Status		S095014 Lyophilizate
Included	**n**	**74**
in compliance with the protocol	n (%)	73 (98.6)
with a protocol deviation before or at inclusion	n (%)	1 (1.4)
Withdrawn from study due to	**n (%)**	**22 (29.7)**
adverse event	n (%)	18 (24.3)
physician decision	n (%)	4 (5.4)
Completed	**n (%)**	**52 (70.3)**
in compliance with the protocol	n (%)	38 (51.4)
with a protocol deviation after inclusion	n (%)	14 (18.9)

% are based on N.
Source: Table 14.1.1.1

In the SAS, the mean age (± SD) at baseline was 6.1 ± 3.8 years (min - max: 2 - 18), with 81.1% aged < 10 years old and 97.3% aged < 16 years old. Male patients represented 51.4% of the SAS. The majority of patients were of Caucasian origin (95.9%). The mean (± SD) BMI was 16.45 ± 3.51 kg/m2 and mean (± SD) BSA was 0.90 ± 0.36 m2. Most patients (62.2%) had an ECOG PS of 1 at baseline.
All of the investigators decided to administer pegaspargase at a dose of 1000 U/m², over a1-hour IV infusion (on weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27). A single dose was received by 7 patients, 2 doses only were received by 10 patients, and 3 doses only were received by 3 patients. Thus, 20/74 patients (27%) received 3 doses or less. Except for 2 patients who received 8 doses, the remaining patients (52/74 [70%]) received 9 doses, as per protocol.

Assessor's comments

In the CL2-095014-003 study, 74 of paediatric patients with age range of 1-18 years were treated with oncaspar at known therapeutic doses (1000, 2000, or 2500 UI/m2) every 2 weeks . 22 were withdrawn from the study among which 18 due to an AE and 4 due to the physician's decision. The AEs leading to the study withdrawal are discussed in the section 2.2.3.

The study paediatric population and indication are in accordance with oncaspar's EU authorised indication scope.

Efficacy results

NA

Safety results

- Adverse events

All 74 (100%) patients of the SAS had at least one TEAE during the study, for a total of 954 events.

There were 56 serious emergent events, but no deaths.

Analysis of TEAEs by frequency

The most frequently affected SOCs were Investigations (59 patients, 79.7%) and Blood and lymphatic systemic disorders (55 patients, 74.3%).

Table (12.1.2) 1 - Treatment emergent AE by System Organ Class - Safety Analysis Set (N = 74)

System Organ Class (SOC)	S95014 Lyophilizate (N = 74)		
	NEAE	n	%
Any Treatment Emergent AE	**954**	**74**	**100.0**
Investigations	501	59	79.7
Blood and lymphatic system disorders	216	55	74.3
Immune system disorders	42	29	39.2
Infections and infestations	71	29	39.2
Metabolism and nutrition disorders	42	21	28.4
Gastrointestinal disorders	19	12	16.2
General disorders and administration site conditions	13	9	12.2
Nervous system disorders	10	9	12.2
Hepatobiliary disorders	11	6	8.1
Musculoskeletal and connective tissue disorders	5	5	6.8
Cardiac disorders	4	4	5.4
Respiratory, thoracic and mediastinal disorders	5	3	4.1
Skin and subcutaneous tissue disorders	5	3	4.1
Vascular disorders	3	3	4.1
Injury, poisoning and procedural complications	2	2	2.7
Renal and urinary disorders	2	2	2.7
Eye disorders	1	1	1.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	1.4
Psychiatric disorders	1	1	1.4

NEAE: Number of treatment emergent adverse events.
n: Number of subjects who had at least one AE in each primary system organ class.
Percentages are based on N.
AEs were coded using MedDRA dictionary version 25.0
Source: Table 14.3.1.5

The most frequently reported PTs (in at least 50% of patients overall) were antithrombin III decreased (53 patients, 71.6%) neutropenia (51 patients, 68.9%) and blood fibrinogen decreased (48 patients, 64.9%).

Table (12.1.2) 2 - Most frequently reported TEAEs (in ≥ 3 patients) by PT - Safety Analysis Set (N = 74)

Preferred term	S95014 Lyophilizate (N = 74)		
	NEAE	n	%
Any Treatment Emergent AE (TEAE)	**954**	**74**	**100.0**
Antithrombin III decreased	161	53	71.6
Neutropenia	111	51	68.9
Blood fibrinogen decreased	118	48	64.9
Alanine aminotransferase increased	48	35	47.3
Anaemia	48	33	44.6
Gamma-glutamyltransferase increased	31	31	41.9
Aspartate aminotransferase increased	28	24	32.4
Hypersensitivity	32	24	32.4
Leukopenia	27	21	28.4
Hypoalbuminaemia	20	14	18.9
Protein S decreased	17	12	16.2
Blood bilirubin increased	11	11	14.9
Neutrophil count decreased	17	11	14.9
Thrombocytopenia	14	11	14.9
COVID-19	10	10	13.5
White blood cell count decreased	8	8	10.8
Activated partial thromboplastin time prolonged	8	7	9.5
Pyrexia	10	7	9.5
Drug hypersensitivity	8	6	8.1
Lipase increased	8	6	8.1
Hypoglycaemia	7	5	6.8
Toxic neuropathy	5	5	6.8
Blood albumin decreased	5	4	5.4
Febrile neutropenia	4	4	5.4
Haemoglobin decreased	4	4	5.4
Hypofibrinogenaemia	6	4	5.4
Upper respiratory tract infection	7	4	5.4
Ammonia increased	3	3	4.1
Amylase increased	3	3	4.1
Back pain	3	3	4.1
Hyperammonaemia	6	3	4.1
Hypertriglyceridaemia	3	3	4.1
Lymphocyte count decreased	3	3	4.1
Lymphopenia	3	3	4.1
Nausea	3	3	4.1
Platelet count decreased	5	3	4.1
Rhinitis	3	3	4.1
Viral upper respiratory tract infection	3	3	4.1

AE: Adverse Event; n: Number of subjects who had at least one AE in each preferred term; NEAE: Number of treatment emergent adverse events; PT: Preferred term.
Percentages are based on N.
AEs were coded using MedDRA dictionary version 25.0.
Source: Table 14.3.1.6

The reported TEAEs were consistent with the known adverse reactions of S95014 and with the underlying pathology (ALL).

Assessor's comments

The table 12.1.2 showed that the most frequently reported PTs are: antithrombin III decreased (53 patients, 71.6%) neutropenia/ Neutrophil count decreased (62 patients, 83,7 %) and blood fibrinogen decreased (48 patients, 64.9%). The MAH concluded that the reported TEAEs are in accordance with the known profile of adverse events with S95014.

According to oncaspar' s SmPC, the AE antithrombin III decreased is not listed in the sections 4.8 and 4.4 of the smpc. In the other hand, neutropenia / Neutrophil count decreased reported in 62 patients,

(83,7%)is listed with unknown frequency in the section 4.8 of the smpc, only febrile neutropenia is considered as very common in the EU SmPC.

The MAH provided as part of the study annexes the listing of Treatment Emergent Adverse Events in the Safety Analysis Set with details concerning AE's seriousness, outcome and severity. According to this data, none of the AEs in relation with antithrombin III decreased were serious, nevertheless, the MAH is requested to discuss the clinical relevance of this AE and the need to update the product smpc accordingly. Moreover, the MAH is requested to discuss the increase of neutropenia/neutrophil count decreased frequencies reported in this study which is not in accordance with Oncaspar's SmPc. This discussion should be based on the cases causality assessment as well as the clinical relevance of those events. Update of the Smpc should be also discussed accordingly.

We noted ,among the most frequently reported PT, the PT toxic neuropathy which concerned 5 different patients. This AE is not listed in the oncaspar smpc, thus, the MAH is requested to provide more details concerning those cases (case narratives with seriousness, causality assessment, action taken with study treatment, outcome and clinical relevance of those events).

Analysis of TEAEs by intensity

Overall, most TEAEs were rated Grade 2 (37.9%) or Grade 3 (39.0%); 11.9% of TEAEs were Grade 4 and none were fatal. Grade 3/4 TEAEs were reported for 72 patients (97.3%).

The most frequent Grade 3/4 events were neutropenia and certain events pertaining to the SOC investigations (concerning mainly coagulation parameters and raised liver enzymes).

Grade 3/4 TEAEs were reported for 72 patients (97.3%).Grade 3/4 TEAEs reported in at least 3 patients are presented in Table (12.1.3) 2 by SOC and PT.

Table (12.1.3) 2 - Most frequently reported Grade 3/4 TEAEs (in ≥ 3 patients) by SOC and PT - Safety Analysis Set (N = 74)

System Organ Class (SOC) Preferred Term (PT)	S95014 Lyophilizate (N = 74)		
	NEAE	n	%
Any Treatment Emergent AE - Grade 3/4	**486**	**72**	**97.3**
Investigations	**262**	**57**	**77.0**
Antithrombin III decreased	101	45	60.8
Alanine aminotransferase increased	36	27	36.5
Gamma-glutamyltransferase increased	27	27	36.5
Blood fibrinogen decreased	30	21	28.4
Neutrophil count decreased	17	11	14.9
Protein S decreased	14	10	13.5
Aspartate aminotransferase increased	6	6	8.1
White blood cell count decreased	4	4	5.4
Activated partial thromboplastin time prolonged	4	3	4.1
Haemoglobin decreased	3	3	4.1
Platelet count decreased	4	3	4.1
Blood and lymphatic system disorders	**161**	**54**	**73.0**
Neutropenia	104	50	67.6
Anaemia	20	17	23.0
Leukopenia	17	15	20.3
Thrombocytopenia	9	7	9.5
Febrile neutropenia	4	4	5.4
Immune system disorders	**18**	**16**	**21.6**
Hypersensitivity	13	12	16.2
Infections and infestations	**20**	**11**	**14.9**
COVID-19	3	3	4.1
Metabolism and nutrition disorders	**11**	**9**	**12.2**
Hypoglycaemia	5	4	5.4
Hypertriglyceridaemia	3	3	4.1
General disorders and administration site conditions	**3**	**3**	**4.1**
Hepatobiliary disorders	**4**	**3**	**4.1**

NEAE: Number of emergent adverse events.
n: Number of patients who had at least one TEAE in the presented primary SOC or PT.
%'s are based on N.
AEs were coded using MedDRA dictionary version 25.0.
Source: Table 14.3.1.11

Assessor's comments

The analysis of TEAEs by severity regardless of the events seriousness revealed that Grade 3/4 TEAEs were reported for 72 (97.3%) patients. No fatal events were reported.

The most frequent Grade 3/4 events were neutropenia (98% of the patients reporting neutropenia AEs), antithrombin III decreased (84% of the patients reporting antithrombin III AEs) and certain events related to the SOC investigations especially ASAT increase (77% of the patients with ASAT increased), gamma-GT increase (87% of patients with gamma-GT increase) and blood fibrinogen decreased (43.75% of patients with blood fibrinogen decreased).

Those results should be interpreted with caution regarding the number of patients included in this study sample and the underlying disease. AEs related to hepatotoxicity are in accordance to the study treatment known safety profile. Nevertheless more clarifications are requested regarding the AEs neutropenia and antithrombin III as discussed previously (section Analysis of TEAEs by frequency).

Analysis of treatment-related emergent adverse events

Relationships of TEAEs were assessed by the investigators as:
-Not related.
-Related to the IMP.
-Related to the backbone therapies.
-Related to the study protocol (except IMP and backbone therapies).

Treatment-emergent AEs related to pegaspargase were frequent, with all patients reporting at least one event with a total of 546 IMP-related TEAEs.

The most frequent IMP-related TEAEs were PTs related to the SOC investigations (mostly concerning blood coagulation) and PTs related to the SOC blood system disorders (low blood cell counts). These were mostly Grade 2 (43.0%) or Grade 3 (39.7%); 11.0% were of Grade 4.

A total of 68 patients (91.9%) had at least one TEAE related to the IMP that was considered to be of Grade 3 or 4 severity. The most frequently reported events of this type were antithrombin III decreased (59.5%), neutropenia (48.6%), and blood fibrinogen decreased (28.4%).

A total of 41 TEAEs were reported for either hypersensitivity, drug hypersensitivity, or anaphylactic reaction (4.3% of all TEAEs) and these affected a total of 28 patients (37.8%). These included 32 events of hypersensitivity in 24 patients (31 events in 23 patients, being related to the IMP), 8 events of drug hypersensitivity in 6 patients (IMP related), and a single event of anaphylactic reaction (IMP related).

Most patients (60, 81.1%) also reported at least one TEAE considered as related to backbone therapies, with a total of 371 events. These also mostly concerned the SOCs blood and lymphatic system disorders, and investigations. There were no TEAEs considered as related to the study protocol.

Table (12.1.3) 3 - Most frequently reported TEAEs considered as related to IMP (in ≥ 3 patients) by SOC and PT - Safety Analysis Set (N = 74)

System organ class Preferred term	S95014 Lyophilizate (N = 74)		
	NEAE	n	%
Any TEAE Related to IMP	**546**	**74**	**100.0**
Investigations	**334**	**54**	**73.0**
Antithrombin III decreased	157	53	71.6
Blood fibrinogen decreased	118	48	64.9
Protein S decreased	12	8	10.8
Blood bilirubin increased	7	7	9.5
Activated partial thromboplastin time prolonged	6	5	6.8
Neutrophil count decreased	7	5	6.8
Aspartate aminotransferase increased	4	4	5.4
White blood cell count decreased	4	4	5.4
Alanine aminotransferase increased	3	3	4.1
Ammonia increased	3	3	4.1
Lipase increased	3	3	4.1
Blood and lymphatic system disorders	**137**	**43**	**58.1**
Neutropenia	72	37	50.0
Anaemia	28	20	27.0
Leukopenia	21	17	23.0
Thrombocytopenia	7	7	9.5
Hypofibrinogenaemia	6	4	5.4
Immune system disorders	**40**	**27**	**36.5**
Hypersensitivity	31	23	31.1
Drug hypersensitivity	8	6	8.1
Metabolism and nutrition disorders	**21**	**8**	**10.8**
Hypoalbuminaemia	9	5	6.8
Hypoglycaemia	5	4	5.4
Hyperammonaemia	6	3	4.1
Hepatobiliary disorders	**5**	**4**	**5.4**
Skin and subcutaneous tissue disorders	**4**	**3**	**4.1**

AE: Adverse Event; IMP: Investigational Medicinal Product; n: Number of patients who had at least one TEAE in the presented primary SOC or PT; NEAE: Number of emergent adverse events; PT: Preferred term; SOC: System organ class; TEAE, Treatment Emergent Adverse Event.
Percentages are based on N.
AEs were coded using MedDRA dictionary version 25.0.
Source: Table 14.3.1.15

Assessor's comments

94,4% (68 out of 72) of patients experienced grade 3/4 TEAEs that were considered as related to the IMP. The most frequently reported events of this type were antithrombin III decreased (59.5%), neutropenia (48.6%), and blood fibrinogen decreased (28.4%).

29 (39%) of patients experienced hypersensitivity reactions (hypersensitivity, drug hypersensitivity, or anaphylactic reaction) and all TEAEs were related to IMP.

Apart from hypersensitivity reactions and blood fibrinogen decreased that are considered as known risks with oncaspar, antithrombin III decreased (not listed in oncaspar SmPC)and neutropenia (listed with undetermined frequency) appear as the most frequently related grade ¾ TEAEs in this study. Thus, the MAH is requested to further discuss the cases in relation with both risks as specified previously (section Analysis of TEAEs by frequency).

Emergent serious adverse events

There were 27 patients (36.5%) who reported at least one emergent SAE during the study, with a total of 56 emergent SAEs.

Most frequently, these events concerned the SOC immune system disorders (14 patients, 18.9%), mostly concerning different types of allergic reactions. This was followed by infections and infestations (11 patients, 14.9%) and blood and lymphatic system disorders (10 patients, 13.5%).

For 14 of these events (11 patients) the upgrade to serious was made by the Sponsor:
-Neutropenia– 6 events: 2 events in one patient in a context of laryngitis; one event in a context of sepsis SAE; one in a context of bronchitis SAE; one in a context of COVID-19 infection SAE; and one in a context of upper respiratory tract infection.
-Febrile neutropenia – 2 events: one in a context of device infection; and one without any underlying pathology, signs or symptoms.
-Ejection fraction decreased 1 event: asymptomatic, but LVEF of 27%.
-Neutrophil count decreased 1 event.
-One event each of sepsis and pneumonia fungal in a patient who had previously reported sepsis.
-One event of haemophagocytic lymphohistiocytosis: in the patient with cellulitis gangrenous.
-One event of leukopenia G4.

Hypersensitivity events (including anaphylaxis) affected a total of 28 patients for 41 events. Among them, 15 events were serious (12 events of hypersensitivity, 2 events of drug hypersensitivity, and the event of anaphylactic reaction; 13 patients affected); all considered to be related to the IMP; all were reported as recovered. As indicated above, a total of 17 patients (23.0%) had an allergic reaction TEAE (related to the IMP) that led to IMP discontinuation (8 of the events were serious). The incidence of hypersensitivity in affected individuals did not appear to be influenced by the formulation of pegaspargase they received in the qualifying study (CL2-95014-002): for 9/28 patients, the induction treatment in the qualifying study was the lyophilized formulation and for 19/28 patients it was the liquid formulation.

Treatment-emergent SAEs considered to be related to pegaspargase affected 16 patients (21,6%) with total of 18 events:

Hypersensitivity: 12 events of 11 patients (14.9%).
Drug hypersensitivity: 2 events in 1 patient (1.4%).
Anaphylactic reaction: 1 event in 1 patient (1.4%).
Oedematous pancreatitis: 1 event in 1 patient (1.4%).
Hepatotoxicity: 1 event in 1 patient (1.4%).
Neutropenia: 1 event in 1 patient (1.4%).

For 10 patients, the action taken was "IMP discontinuation" ; the 8 patients reporting hypersensitivity, and the patients reporting drug hypersensitivity or anaphylactic reaction.

No deaths were reported during the study.

Assessor's comments

Serious adverse events related to IMP concerned 16 patients (21,6%). 15 (83,33%) out of the 18 total number of serious adverse events related to the IMP reported hypersensitivity reactions (hypersensitivity, drug hypersensitivity, or anaphylactic reaction) in 13 patients. among which 10 patients discontinued IMP treatment.

The remaining 3 events reported respectively 1 event of Oedematous pancreatitis, 1 of hepatotoxicity and 1 event of neutropenia in 3 different patients.

Related SAEs reported are in accordance with the known safety profile of oncaspar.

Analysis of emergent adverse events according to action taken

Table (12.1.1) 1 - Summary of adverse events - Safety Analysis Set (N = 74)

Adverse Event Type	S95014 Lyophilizate (N = 74)		
	NAE	n	%
Any AEs	962	74	100.0
Any Treatment Emergent AEs	954	74	100.0
Grade 3/4 TEAEs	486	72	97.3
Serious TEAEs	56	27	36.5
Non-serious TEAEs	898	68	91.9
TEAEs related to IMP	546	74	100.0
Grade 3/4 TEAEs related to IMP	277	68	91.9
Serious TEAEs related to IMP	18	16	21.6
TEAEs Leading to IMP Withdrawal	18	18	24.3
TEAEs Leading to IMP Dose Modification	0	0	0.0
TEAEs Leading to IMP Interruption	9	9	12.2
TEAEs Leading to IMP Delay	10	4	5.4
TEAEs Leading to Death	0	0	0.0
TEAEs Requiring New Treatment or Increase of on-going Treatment	381	67	90.5
TEAEs Requiring Surgical or Medical Procedure	8	5	6.8

IMP: Investigational Medicinal Product; n: Number of subjects who had at least one AE in each AE type; NAE: Number of adverse events; TEAE: Treatment emergent adverse event.
Percentages are based on N.
Treatment emergent serious AE related to IMP include sponsor upgrade.
AEs were coded using MedDRA dictionary version 25.0.
Source: Table 14.3.1.1.

Treatment-emergent adverse events leading to treatment discontinuation affected 18 patients (24.3%; for 18 events):

Table (12.2.3) 1 - TEAEs leading to IMP discontinuation by SOC and PT - Safety Analysis Set (N = 74)

System Organ Class (SOC) Preferred Term (PT)	S95014 Lyophilizate (N = 74)		
	NEAE	n	%
Any treatment emergent AE leading to IMP withdrawal	**18**	**18**	**24.3**
Immune system disorders	**17**	**17**	**23.0**
Hypersensitivity	14	14	18.9
Drug hypersensitivity	2	2	2.7
Anaphylactic reaction	1	1	1.4
Blood and lymphatic system disorders	**1**	**1**	**1.4**
Agranulocytosis	1	1	1.4

IMP: Investigational Medicinal Product; n: Number of subjects who had at least one AE in each primary system organ class or preferred term; NEAE: Number of treatment emergent adverse events.
Percentages are based on N.
Treatment emergent AE related to IMP include sponsor upgrade.
Adverse events were coded using MedDRA dictionary version 25.0.
Source: Table 14.3.1.51

A total of 67 patients (90.5%) reported a TEAE requiring additional therapy. In addition, 5 patients (6.8%) reported a total of 8 TEAEs requiring a surgical or medical procedure.

In addition, 4 patients were withdrawn from treatment due to the investigator's decision:
Patient 1: had hypersensitivity reactions (3 events), of grade 1 or 2 and was withdrawn on day 64.
Patient 2: had a drug hypersensitivity reaction and a hypersensitivity reaction (2 separate visits), of grade 2 and was withdrawn on day 56.
Patient 3: had numerous TEAEs (mostly under the SOC investigations) but more importantly neutropenic sepsis (2 events), cellulitis gangrenous and haemophagocytic lymphohistiocytosis (all 4 events were SAE); the action taken was "new treatment or dose modification of ongoing treatment other than IMP and backbone therapies" and the patient was withdrawn on day 246.
Patient 4: had several blood related disorders (grade 2 or 3) including neutropenia,anaemia, hypertriglyceridaemia, as well as increased liver enzymes. A change of treatment protocol was advised at W11 and the patient was withdrawn.

Assessor's comments

We noted 18 patients with AEs leading to treatment withdrawal. 17 out of 18 treatment withdrawals were related to hypersensitivity reactions. 10 out of the 17 events /patients were serious adverse events related to IMP. The risk of hypersensitivity and anaphylactic reaction is known with oncaspar and considered as a very common risk. Thus, no new signal emerges from the provided data.

- Clinical laboratory results

Emergent abnormal laboratory values were generally reported as AEs and analyzed as such. There were no unexpected changes observed in the mean values of observed parameters.

The mean values for biochemistry parameters were generally consistent with ALL.

Clinically significant abnormal values

The most frequently reported emergent Grade ≥ 3 abnormal values concerned GGT (32 patients overall, 43.2%), ALT (25 patients, 33.8%) and hypertriglyceridemia (14 patients, 18.9%). No emergent Grade ≥ 3 values were observed for bicarbonate, glucose, alkaline phosphatase, creatinine or lactate dehydrogenase.

The most frequently reported emergent Grade ≥ 3 abnormal values concerned anemia (16 patients, 21.6%; all Grade 3), white blood cells decreased (16 patients overall, 21.6%), hemoglobin increased (10 patients, 13.5%) and low lymphocyte counts (9 patients overall, 12.2%).

The most frequently reported emergent Grade 3 values concerned low fibrinogen levels (16 patients, 21.6%). There were no Grade 4 events.

- Vital signs and ECOG PS

The assessments of vital signs (systolic and diastolic BP, HR and body temperature) indicated no clinically relevant differences over time from baseline. There was no deterioration in ECOG PS over time. The analyses of the change in systolic and diastolic BP, HR and body temperature, from baseline to each visit as well as baseline to withdrawal/end-of-study show no meaningful trends or issues

Assessor's comments

The most frequently reported emergent Grade ≥ 3 abnormal values are in line with the known safety profile of S95014. No grade 4 values were reported. We noted also no deterioration in ECOG performance status over time. However, the MAH did not mention the antithrombine III decreased among the most frequently reported abnormal values while it was reported as the most frequently Grade 3/4 events. This should be clarified.

Conclusion on Safety

No new safety concerns for S95014 were detected and it was well tolerated. No fatal events were reported during the study. Hypersensitivity reactions were the main AE leading withdrawal of the study treatment, with a total of 17 patients (23.0%) being withdrawn for these reactions. The safety profile observed in this study is consistent with the known safety profile of pegaspargase.

2.2.3. Discussion on clinical aspects

The CL2-95014-003 study was a "roll-over" study, designed to provide continued access to S95014 during the consolidation phase in patients who completed the CL2-95014-002 study and who were clinically benefitting from S95014 without major toxicity. The CL2-95014-003 study was initiated on the May 15th, 2021 and completed on January 23rd, 2023.

No efficacy or PK endpoints were assessed and the safety endpoints were analysed in the Safety Analysis Set (SAS).

The study planned to enroll 75 patients. Overall 74 patients were treated and analysed. The study duration was approximately 7 months, including the treatment and follow-up periods. In the SAS, the mean age (± SD) at baseline was 6.1 ± 3.8 years (min - max: 2 - 18), with 81.1% aged < 10 years old and 97.3% aged < 16 years old. Male patients represented 51.4% of the SAS. The majority of patients were of Caucasian origin (95.9%).

Pegaspargase was administered every two weeks during the consolidation phase for a total of 9 infusions, Patients also received other backbone chemotherapy agents as per the ALL-MB 2015 protocol. 20/74 patients (27%) received 3 doses or less. Except for 2 patients who received 8 doses, the remaining

patients (52/74 [70%]) received 9 doses, as per protocol. After completing the consolidation phase, patients were discontinued from the study and treated as per investigator's judgment.

22 (29.7%) were prematurely withdrawn: 18 due to an adverse event and 4 due to the physician's decision.

Regarding the safety results, all 74 (100%) patients of the SAS had at least one TEAE during the study, for a total of 954 events. There were 56 serious emergent events, none fatal.

The most frequently affected SOCs were Investigations (59 patients, 79.7%) and Blood and lymphatic systemic disorders (55 patients, 74.3%). Overall, most TEAEs were rated Grade 2 (37.9%) or Grade 3 (39.0%); 11.9% of TEAEs were Grade 4 and none was fatal. Nevertheless, Grade 3/4 TEAEs were reported for 72 patients (97.3%) and 94,4% (68 out of 72) of patients experienced grade 3/4 TEAEs that were considered as related to the IMP. Those results should be interpreted with caution because of the study sample size and the patient's underlying disease.

The most frequently reported PTs are: antithrombin III decreased (53 patients, 71.6%) neutropenia/ Neutrophil count decreased (62 patients, 83,7 %) and blood fibrinogen decreased (48 patients, 64.9%).

According to oncaspar' s SmPC, Only blood fibrinogen decreased is listed with frequency "very common" in oncaspar Smpc. the AE antithrombin III decreased is not listed in the sections 4.8 and 4.4 of the smpc. In the other hand, neutropenia / Neutrophil count decreased reported in 62 patients, (83,7%)is listed with unknown frequency in the section 4.8 of the smpc and only febrile neutropenia is considered as very common in the EU SmPC.

The MAH is requested to discuss the clinical relevance of AEs reporting antithrombin III decreased with regard to the cases causality assessment and severity in order to evaluate the need to update the product smpc accordingly. Moreover, the MAH is also requested to discuss the increase of neutropenia/neutrophil count decreased's frequency reported in this study which is not in accordance with Oncaspar's SmPc. This discussion should be based on the cases causality assessment as well as the clinical relevance of those events. Smpc 's update should be also discussed accordingly.

Toxic neuropathy were reported among the most frequently reported PT in this study and was reported in 5 patients. Considering that this AE is not listed in the oncaspar smpc,, the MAH is requested to provide more details concerning those cases (case narratives with seriousness, causality assessment, action taken with study treatment, outcome and clinical relevance of those events).

29 out of 74 (39%) patients experienced hypersensitivity reactions (hypersensitivity, drug hypersensitivity, or anaphylactic reaction) and all TEAEs were related to IMP.

Serious adverse events related to IMP concerned 16 patients (21,6%). 15 (83,33%) out of the 18 total number of serious adverse events related to the IMP reported hypersensitivity reactions.

We noted 18 patients with AEs leading to treatment withdrawal. 17 out of 18 treatment withdrawals were related to hypersensitivity reactions. 10 out of the 17 events /patients were serious adverse events related to IMP.

Hypersensitivity reaction (HSR) concerned 39% of the patients (29 patients) among which 55% reported serious related adverse events. 34.5% of the patients (10 patients) with HSR reactions have been discontinued due to these SAEs. HSR are a known risk of oncaspar and are listed in the SmPC with frequency "very common". The results of this study doesn't reveal a new trend concerning this risk.

With regards to lab data, the most frequently reported emergent Grade ≥ 3 abnormal values are in line with the known safety profile of S95014. No grade 4 values were reported. However, the MAH did not mention the antithrombine III decreased among the most frequently reported abnormal values while it was reported as the most frequently Grade 3/4 events. This should be clarified.

We noted also no deterioration in ECOG performance status over time.

3. Overall conclusion and recommendation

The safety results of lyophilized Oncaspar in the CL2-095014-003 paediatric study should be interpreted with caution regarding the study descriptive design, the population sample size and the underlying disease. Moreover, more clarifications are needed from the MAH to better conclude about the SmPC amendments required at this stage.

☐ **Fulfilled**

☒ **Not fulfilled**

Based on the data submitted, the MAH should provide clarification for considering the reported TEAEs as consistent with the known adverse reactions of S95014 as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information (RSI)

4.1. Major objections

NA

4.2. Other concerns

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1) Low antithrombin activity is considered as the most frequently reported AEs with oncaspar in this study. Of note, results of the previous study, CL2-095014-002 showed also a higher frequency of Low antithrombin activity with lyophilized formulation (LYO) of Oncaspar® compared to the liquid formulation.
   According to oncaspar's SmPC, the AE antithrombin III decreased is not listed in the sections 4.8 and 4.4 of the smpc. The MAH is requested to discuss the clinical relevance of AEs reporting antithrombin III decreased with regard to the cases causality assessment and severity in order to evaluate the need to update the product smpc accordingly.
2) The MAH is also requested to discuss the increase of neutropenia/neutrophil count decreased frequency reported in this study which is not in accordance with Oncaspar's SmPc. This discussion should be based on the cases causality assessment as well as the clinical relevance of those events. Update of Smpc should be also discussed accordingly.
3) Toxic neuropathy were reported among the most frequently reported PT in this study and concerned 5 patients. Considering that this AE is not listed in the oncaspar smpc, the MAH is requested to provide more details concerning those cases (case narratives with seriousness, causality assessment, action taken with study treatment, outcome and clinical relevance of those events).

4.3. MS comment

MS comment:

RSI question 1 is supported. Furthermore, in the previously reported phase 2 clinical study, CL2-095014-002, where lyophilized formulation (LYO) of Oncaspar® was compared against the liquid formulation (LIQ), the frequency of Low antithrombin activity was seen more often in the LYO group than the LIQ group: 35/43 patients (81.4%) versus 27/43 patients (62.8%) at Day 10; 35/41 patients (85.4%) versus 25/43 patients (58.1%) at Day 17; and 26/41 patients (63.4%) versus 17/42 patients (40.5%) at Day 24. The applicant should also discuss the possible reasons for this difference in frequencies between the two formulations and the clinical relevance of this finding.

In addition, the results of the studies CL2-095014-002 and CL2-095014-003 should be discussed within the next PSUR, particularly with respect to the detected inconsistencies' with the current SmPC of Oncaspar.

Rapp comment
Rapp thanks the MS for the raised comment. It's agreed that the results of the study CL2-095014-002 showed higher frequency of Low antithrombin activity with lyophilized formulation (LYO) of Oncaspar® compared to the liquid formulation. Nevertheless, in the CL2-095014-003 study, the study design and treatment regimen are different (non- comparative study, different study drug dosage), thus we would suggest to keep the question focused on the latter study context and results.
Moreover, as suggested, further discussion is anticipated in the next PSUR.

The timetable is a 30 day response timetable without clock stop

4.4. MAH responses to Request for supplementary information

Question N°1:

Low antithrombin activity is considered as the most frequently reported AEs with oncaspar in this study. Of note, results of the previous study, CL2-095014-002,showed also a higher frequency of Low antithrombin activity with lyophilized formulation (LYO) of Oncaspar® compared to the liquid formulation. According to oncaspar's SmPC, the AE antithrombin III decreased is not listed in the sections 4.8 and 4.4 of the smpc. The MAH is requested to discuss the clinical relevance of AEs reporting antithrombin III decreased with regard to the cases causality assessment and severity in order to evaluate the need to update the product smpc accordingly.

MAH's response:

In study CL2-95014-003, 74 patients were treated with Oncaspar lyophilized formulation. One hundred and fifty-seven (157) "antithrombin III decreased" treatment emergent adverse events (TEAEs) related to Oncaspar (i.e., related to Oncaspar only or to Oncaspar and backbone therapy) were reported for 53 patients, which represents 71.6% of treated patients. This is indeed the most frequent related TEAEs for this study. None of these AEs were reported as serious. Among the 53 patients, 31 had received corticosteroids (dexamethasone, methylprednisolone, prednisolone) to prevent or relieve allergic reactions while under treatment with Oncaspar. This observation is aligned with current EU SmPC Section 4.5: When glucocorticoids (e.g., prednisone) and pegaspargase are given at the same time, alterations in coagulation parameters (e.g., fall in fibrinogen and antithrombin III deficiency, ATIII) can be more pronounced. For the remaining 22 patients, no glucocorticoid was taken as concomitant medication. Yet, all patients were treated with dexamethasone as part of the backbone therapy of the ALL-MB 2015 protocol.

In study CL2-95014-002, 88 patients received one infusion of Oncaspar (43 with lyophilizate formulation and 45 with liquid formulation). Fifty-nine (59) "antithrombin III decrease" TEAEs related to Oncaspar

were reported for 59 patients (one event per patient), which represents 67% of treated patients. Among the 59 AE, 31 AEs for 31 patients are reported in the lyophilized arm (72.1% of patients) and 28 AEs for 28 patients (62.2% of patients) are reported in the liquid arm. This AE is the second most frequent related TEAE of this study, whatever the treatment arm. Similarly to study CL2-95014-003, 5 patients among the 59 received corticosteroids while under treatment with Oncaspar (3 from the lyophilized arm, and 2 from the liquid arm) and all patients received dexamethasone as part of ALL-MB 2015 protocol. There were 3 treatment-related serious adverse events (SAEs) of antithrombin III decreased reported for 3 patients (3.4% of treated patients): they were not reported as serious by investigators, and were upgraded to "serious" by the sponsor. These three related SAE were of Grade 4 in severity and concerned 2 patients in the lyophilized arm and 1 patient in the liquid arm.

Thus, occurrence of "Antithrombin III decreased" in both studies is related to Oncaspar but two factors could partly explain the relatively high occurrence in these trials:

- intake of glucocorticoids as concomitant medication or as part of the backbone chemotherapy agents outlined in the ALL-MB 2015 protocol on top of Oncaspar,
- ALLMB 2015 protocol requiring a measurement of antithrombin III levels before each infusion (MB-protocol section 29.8 / 29.13), which can lead to a higher AE detection compared to other protocols using asparaginase at same dose of 1000 IU/m2 (e.g. the UKALL and NOPHO protocols require follow-up of thromboembolism AEs but not specifically level in antithrombin III before each infusion).

Currently, risks of "coagulopathy" and "blood fibrinogen decreased" associated with Oncaspar are listed in the EU SmPC sections 4.4 and 4.8. It is also mentioned in section 4.4: "When there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy". The risk of antithrombin III decreased is reported when Oncaspar is associated with glucocorticoids in the EU SmPC section 4.5.

Despite these potential reasons, relationship to Oncaspar cannot be ruled out. Therefore, the MAH agrees to add AE "Antithrombin III decreased" based on frequency observed in the CL2-95014-002 and CL2-95014-003 studies. As the frequency of antithrombin III AE related to Oncaspar is 67% of treated patients (59 over 88 treated patients) in the 002 study, and 71.6 % of patients (53 over 74 patients) in the 003 study. Thus, the MAH proposes to add the AE "antithrombin III decrease" with the frequency "very common" (frequency ≥1/10) in section 4.8 of the EU SmPC.

Proposed Updates of the Product Information:

MAH proposes to update sections 4.4 and 4.8 of the EU SmPC of Oncaspar as follows:

4.4 Special warnings and precautions for use

(…)

Coagulopathy
Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving pegaspargase (see section 4.8). Oncaspar should be discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia **and antithrombin III decrease** can occur in patients receiving pegaspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment, particularly when other medicinal products with anticoagulant effects (such as acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products) are used simultaneously (see section 4.5), or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered. When

there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions described in this section are derived from clinical studies data and post-marketing experience of Oncaspar in ALL patients. The safety profile is based on randomised, controlled, prospective, open label multicentre studies using Oncaspar at a dose of 2500 U/m2 administered intravenously as a comparative treatment (studies DFCI 11-001 and AALL07P4). In addition, the safety profile included data from other Oncaspar studies such as the study comparing the pharmacokinetics of the liquid and the lyophilized formulations of pegaspargase (CL2-95014-002), its roll-over study (CL2-95014-003) and studies using the intramuscular route of administration (studies CCG-1962 and CCG-1991) (see section 5.1 for CCG-1962 and CCG-1991).

(…)

Table 1: Adverse reactions reported with Oncaspar therapy

MedDRA standard system organ class	Adverse reaction
Investigations	Very common: Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased, amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased, **antithrombin III decreased****

**** See the text in question 2.

The MAH proposes not to update the Patient Leaflet because blood clots are mentioned as "very common" in section 4 "possible side effects". In addition, a warning about the risk of coagulopathy is explained in section 2 under paragraph "Warnings and precautions" as follows:
"This medicine can lead to fluctuations in clotting factors and may increase the risk of bleeding and/or clotting."

Assessor's comments

The MAH confirmed that "antithrombin III decreased" treatment emergent adverse events (TEAEs) are the most frequent related TEAEs with oncaspar in both studies CL2-95014-003 and CL2-95014-002 and proposed consequently an update of the oncaspar smpc in order to include this risk in the section 4.4 as follows:

Coagulopathy:

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving pegaspargase (see section 4.8). Oncaspar should be discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia ***and antithrombin III decrease*** *can occur in patients receiving pegaspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment, particularly when other medicinal products with anticoagulant effects (such as acetylsalicylic acid and non-steroidal anti-*

inflammatory medicinal products) are used simultaneously (see section 4.5), or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered.

When there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

The MAH proposed also to update the section 4.8 in order to add the risk of "antithrombin III decreased" among the most commonly reported AEs in the SOC "investigations" according to the recent clinical studies (CL2-95014-002 and CL2-95014-003) data.

We agree with the MAH's proposal to update both product SmPC's sections 4.4 and 4.8.

The MAH should submit a relevant variation in a timely manner to update the product SmPC accordingly.

Question N°2:

The MAH is also requested to discuss the increase of neutropenia/neutrophil count decreased frequency reported in this study which is not in accordance with Oncaspar's SmPC. This discussion should be based on the cases causality assessment as well as the clinical relevance of those events. Update of Smpc should be also discussed accordingly.

MAH's response:

In study CL2-95014-003, 74 patients were treated with Oncaspar. Seventy-two (72) "neutropenia" TEAEs related to Oncaspar (i.e. related to Oncaspar only or to Oncaspar and backbone therapy) were reported for 37 patients, which represents 50.0% of treated patients. Seven (7) "neutrophil count decreased" TEAEs related to Oncaspar (i.e., related to Oncaspar only or to Oncaspar and backbone therapy) were reported for 5 patients, which represents 6.8% of treated patients. Thus, the total frequency of "neutropenia" and "neutrophil count decrease" related to Oncaspar is 56.8% of treated patients (42 patients with these related TEAEs over 74 treated patients).

The 72 related TEAEs with preferred term "neutropenia" were of grade 2 to 4 and all reported as non-serious except for one patient where event "neutropenia" of grade 4 seriousness was upgraded by the sponsor to "serious" as following an event of sepsis. The 7 TEAEs with preferred term "neutrophil count decreased" were of grade 3 to 4 and all reported as non-serious AEs associated with neutropenia/neutrophil count decreased are reported with no associated symptom. No action taken with study treatment (referred as "IMP" in the CSR) was reported for these events. Thus, these AEs do not have a significant clinical relevance on patients.

Considering the overall frequency of 56.8% for treatment-related neutropenia and neutrophil count decreases reported in the CL2-95014-003 study, the MAH agrees to update the frequency of neutrophil count decrease in the Oncaspar SmPC from "not known" to "very common" (frequency ≥1/10) in section 4.8 of the EU SmPC. As neutropenia is a synonym of neutrophil counts decrease, only neutrophil count decrease terminology is used for update in the Oncaspar EU SmPC.

Proposed Updates of the Product Information:

The MAH proposes to update section 4.8 of the EU SmPC of Oncaspar as follows:

4.8 Undesirable effects

(…)

Table 1: Adverse reactions reported with Oncaspar therapy

MedDRA standard system organ class	*Adverse reaction*

Investigations	*(…)* *Very common: Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased, amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased, antithrombin III decreased****, **neutrophil count decreased****** *Not known: Blood urea increased, anti pegaspargase antibodies, neutrophil count decreased, platelet count decreased, hyperammonaemia*

******* Cases of antithrombin III and neutrophil count decreased were observed in CL2-95014-002 and CL2-95014-003 studies***

In addition, the MAH proposes to update the corresponding section of the patient leaflet of the Product Information in section 4 "possible side effects" - "Other side effects" as follows:

Other side effects

Talk to your doctor if you get any of the following:

Very common (may affect more than 1 in 10 people)
- *Changes in the function of the pancreas;*
- *Weight loss;*
- *Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism);*
- *Loss of appetite, general weakness, vomiting, diarrhoea, nausea;*
- *Increased blood sugar levels;*
- ***Decreased number of white blood cells.***

Not known (frequency cannot be estimated from the available data)
- *Decreased number of white blood cells and platelets;*

(…)

Assessor's comments

The MAH confirmed that 50% of the CL2-95014-003 study population experimented neutropenia/neutrophil count decreased related to oncaspar and proposed to amend the frequency of this risk in the section 4.8 from "not known" to "very common". Moreover, the MAH proposed to amend the section 4 of the patient's leaflet accordingly. The MAH's proposals FOR SmPC update are endorsed.

The MAH should submit a relevant variation in a timely manner to update the product SmPC accordingly.

Question N°3:

Toxic neuropathy were reported among the most frequently reported PT in this study and concerned 5 patients. Considering that this AE is not listed in the oncaspar smpc, the MAH is requested to provide

more details concerning those cases (case narratives with seriousness, causality assessment, action taken with study treatment, outcome and clinical relevance of those events).

MAH's response:

In the study CL2-95014-003, 5 "toxic neuropathy" TEAE were reported for 5 patients, which represent 6.8% of treated patients. None of the cases of toxic neuropathy reported were related to Oncaspar. Summary information contained in CSR listing provide the following information: preferred term, grade, start/stop dates, seriousness, causality assessment, outcome, and action taken with study treatment. All AEs were reported as related to the backbone therapies, mostly vincristine, for which neurotoxicity is a known AE. These AE severities varied from grade 1 to 2 and were reported as "non-serious". No dose interruption or dose modification of Oncaspar occurred due to these events. All AE are recovered, and no sequelae was reported. No narrative is available for these events as they did not meet criteria for narrative writing (criteria such as death, serious AE, event of special interest, AE leading to study treatment discontinuation).

Oncaspar EU SmPC contains information regarding central nervous system disorders:
- Section 4.4: "Oncaspar may cause central nervous system signs and symptoms manifesting as somnolence, confusion, convulsions. Patients should be closely monitored for such symptoms, especially if Oncaspar is used in association with neurotoxic products (such as vincristine and methotrexate; see section 4.5);
- section 4.5: "Immediately preceding or simultaneous treatment with vincristine can increase the toxicity of pegaspargase. Administration of Oncaspar before vincristine may increase the neurotoxicity of vincristine. Therefore, vincristine should be given at least 12 hours prior to administration of Oncaspar in order to minimise toxicity.",
- section 4.8: "peripheral motor neuropathy" is listed,

In summary, AE of toxic neuropathy are reported by investigators as not related to Oncaspar but rather to concomitant chemotherapy known to induce neurotoxicity. Thus, the MAH proposes not to add the AE "toxic neuropathy" to the EU SmPC.

Assessor's comments

The MAH clarified that the 5 cases of toxic neuropathy were not serious, not related to oncaspar and didn't require oncaspar's interruption or dose modification. The narratives were not provided because the cases did not meet criteria for narrative writing. The MAH added also that neurological disorders are adequately described in oncaspar's SmPC (section 4.4, 4.5 and 4.8).

The MAH's response is approvable.

4.5. Discussion on clinical aspects after first RSI assessment

The MAH was requested to discuss the clinical relevance of AEs reporting antithrombin III decreased with regard to the cases causality assessment and severity in order to evaluate the need to update the product smpc accordingly. Moreover, the MAH was also requested to discuss the increase of neutropenia/neutrophil count decreased's frequency reported in this study which is not in accordance with Oncaspar's SmPc. The MAH confirmed as part of the RSI responses that "antithrombin III decreased" treatment emergent adverse events (TEAEs) are the most frequent related TEAEs with oncaspar in both studies CL2-95014-003 and CL2-95014-002 and proposed consequently an update of the oncaspar smpc in order to include this risk in the section 4.4 and in the section 4.8 of the SmPC. In the other hand, the MAH confirmed that 50% of the CL2-95014-003 study population experimented neutropenia/neutrophil count decreased related to oncaspar and proposed to amend the frequency of this risk in the section 4.8 from "not known" to "very common" and to amend the PL accordingly.

Toxic neuropathy was reported among the most frequently reported PT in this study and was reported in 5 patients. Considering that this AE is not listed in the oncaspar SmPC, the MAH was requested to provide more details concerning those cases (case narratives with seriousness, causality assessment, action taken with study treatment, outcome and clinical relevance of those events). The MAH clarified that the 5 cases of toxic neuropathy were not serious, not related to Oncaspar and didn't require oncaspar's interruption or dose modification. The narratives were not provided because the cases did not meet criteria for narrative writing. The MAH added also that neurological disorders are adequately described in oncaspar's SmpC (section 4.4, 4.5 and 4.8).

The proposed change in the SmPC are agreed and the relevant variation to include them as per general guidance on P46 procedure should be provided in a timely manner.

5. Overall conclusion and recommendation after first RSI

The safety results of lyophilized Oncaspar in the CL2-095014-003 paediatric study should be interpreted with caution regarding the study descriptive design, the population sample size and the underlying disease. SmPc amendments were proposed by the MAH as part of RSI response and are approved. The MAH should submit a relevant variation in a timely manner to update the product SmPC accordingly.

☒ **Fulfilled**