2. SYNOPSIS

Name of Sponsor: I.R.I.S. & L.L.S., 50 rue Carnot - 92284 Suresnes Cedex – France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** ONCASPAR® **Name of Active Ingredient:** PEGASPARGASE (S95014)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: A multicenter, roll-over study to provide continued treatment with lyophilized pegaspargase (S95014) in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) **Protocol No.:** CL2-95014-003 **EudraCT No.:** 2020-004895-17 **Investigational New Drug Application No.:** 152433		
Main Investigator [redacted]		
Study countries: One country (Russia) with 7 sites.		
Publication (reference): Not applicable		
Studied period: Initiation date: 15 May 2021 Completion date: 23 January 2023	**Phase of development of the study:** II	
Objectives: <u>Primary objective</u> To provide treatment with lyophilized S95014 in pediatric patients with ALL who completed the CL2-95014-002 study during the induction phase. <u>Secondary objectives</u> To assess the safety profile of S95014 during the consolidation phase.		
Methodology: This was a multicenter, non-randomized, roll-over study of lyophilized pegaspargase (Oncaspar®, S95014) in the treatment of pediatric patients with ALL. This study was 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 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. Patients were planned to receive S95014 intravenously at weeks 7, 9, 11, 15, 17, 19, 23, 25, and 27 (9 infusions). The dose to be administered was at the discretion of the investigator; either 1000, 2000 or 2500 U/m² of body surface area (BSA). Patients also received other backbone chemotherapy agents as per the Childhood ALL Protocol Moscow-Berlin 2015 (ALL-MB 2015) and local practice.		
Number of patients: Actual: 75 informed consents were signed; 74 patients were treated and analyzed.		

Diagnosis and main criteria for inclusion and exclusion:

- Patients who completed the CL2-95014-002 study.
- Patients currently receiving clinical benefit from previous treatment with S95014 as per investigator's judgment.
- Signed informed consent and assent (where appropriate).
- Highly effective contraception method.

Main exclusion criteria were any significant laboratory abnormality or uncontrolled intercurrent illness, history of sensitivity to polyethylene glycol (PEG) or PEG-based drugs, or any major safety issue due to previous S95014 administration.

Test drug:
Investigational Medicinal Product (IMP): pegaspargase (S95014), lyophilized formulation.
Unit Dosage: 3750 U per 5 mL vial after reconstitution with 5.2 mL of sterile water for injection.

Comparator (Reference product):
Not applicable

Duration of treatment:
The study duration was approximately 7 months, including the treatment period consisting of the consolidation phase (approximately 6 months) and the follow-up period (30 days after the last S95014 infusion). After completing the consolidation phase, patients were discontinued from the study and treated as per investigator's judgment.

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.

Statistical methods:
Safety Analysis Set (SAS) comprised all patients who had received at least one dose of IMP.
Safety was summarized using descriptive statistics.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

The SAS comprised 74 patients. Of these, 52 (70.3%) completed the study. A total of 22 patients were prematurely withdrawn: 18 (24.3%) due to an adverse event and 4 (5.4%) due to the investigator's decision (directly or indirectly due to adverse events [see safety section]). No patient was lost to follow-up.

BASELINE CHARACTERISTICS

The mean age (± SD) of patients in the SAS was 6.1 ± 3.8 years (min - max: 2 – 18 years old). Male patients represented 51.4% of the SAS. The majority of patients were of Caucasian origin (95.9%). Baseline clinical laboratory values were consistent with ALL.

EXTENT OF EXPOSURE

All 74 patients received at least one dose of S95014 (1000 U/m²). 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.
The mean (±SD) duration of treatment was 5.0 ± 2.59 months and the number of doses administered was 7.0 ± 3.23 (median: 9). The relative dose intensity was 0.7 ± 0.21.

SAFETY RESULTS

The following table presents a summary of the incidence of each category of adverse event and the number of events reported. All 74 patients (100%) of the Safety Analysis Set had at least one TEAE during the study, for a total of 954 events.

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

	S95014 Lyophilizate (N = 74)		
Adverse Event Type	**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.
Adverse events were coded using MedDRA dictionary version 25.0.
Source Table 14.3.1.1.

Treatment emergent adverse events

- There were no deaths during the study.
- At least one TEAE considered as related to the IMP was reported by all patients (74; 100%). These most frequently concerned PTs related to blood coagulation (SOC investigations) and low blood cell counts (SOC blood system disorders). A total of 68 patients (91.9%) had at least one Grade 3/4 TEAE related to the IMP. The most frequently reported events 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). In all, 15 of these events (in 13 patients) were serious (12 events of hypersensitivity, 2 events of drug hypersensitivity, and the event of anaphylactic reaction); all considered to be related to the IMP. The study protocol was not designed to investigate nor explain hypersensitivity cases: plasma asparaginase activity was assessed as per local practice, and prophylactic treatment for hypersensitivity was administered as per local practice and the ALL-MB 2015 protocol.
- At least one emergent SAE was reported for 27 patients (36.5%) for a total of 56 events. Of these, 18 events were considered to be related to the IMP, reported by 16 patients (21.6%). These related events mostly concerned the SOC immune system disorders (13 patients, 17.6%; 15 allergic reaction events) with, in addition, one event each of neutropenia, odematous pancreatitis and hepatotoxicity.
- A total of 18 patients had a TEAE leading to IMP discontinuation (24.3%; 18 events). For 17 patients (23.0%) the event was an allergic reaction related to the IMP (8 events being serious). The remaining event was an agranulocytosis considered to be related to backbone therapies. In addition, 4 patients were withdrawn from treatment due to the investigator's decision.

Clinical laboratory results: No clinically relevant changes in mean values were observed.

Vital signs and ECOG PS: No clinically relevant changes were observed. There was no deterioration in ECOG PS at the last visit compared to baseline.

CONCLUSION

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 to 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.

Date of the report: 30 June 2023

Version of the report: Final version