2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France
Local sponsor: L.L.S. 7, Lesnaya st., Moscow 125196</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
ONCASPAR®

Name of Active Ingredient:
PEGASPARGASE (S95014)</td><td></td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study: A Multicenter, Phase II Randomized study, Open-label, with 2-arm Parallel Group, comparing the Pharmacokinetics of the Liquid and the Lyophilized Formulations of Pegaspargase (S95014) in Treatment of Pediatric Patients with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)
Protocol No.: CL2-95014-002
EudraCT No.: 2020-004894-29
Investigational New Drug Application No.: 152433</td></tr>
<tr><td colspan="3">Main Investigator
[redacted]</td></tr>
<tr><td colspan="3">Study countries:
One country (Russia) included 89 patients across 7 sites.</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 6 May 2021
Completion date: 20 May 2022</td><td>Phase of development of the study:
II</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary objective</u>
To compare the pharmacokinetics (PK) of both lyophilized (LYO) and liquid (LIQ) S95014 formulations during the induction phase after a single intravenous (IV) dose in newly diagnosed pediatric patients with acute lymphoblastic leukemia (ALL).
<u>Secondary objectives</u>
- To describe the PK of S95014 after administration of either LYO or LIQ formulation.
- To evaluate the occurrence of treatment emergent adverse events (TEAEs) including serious adverse events (SAEs), regardless of causality and severity, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 5.0.
- To evaluate the achievement of plasma asparaginase activity (PAA) of ≥ 100 mU/mL after the administration of either LYO or LIQ S95014.
- To assess the immunogenicity of both LYO and LIQ S95014 formulations.</td></tr>
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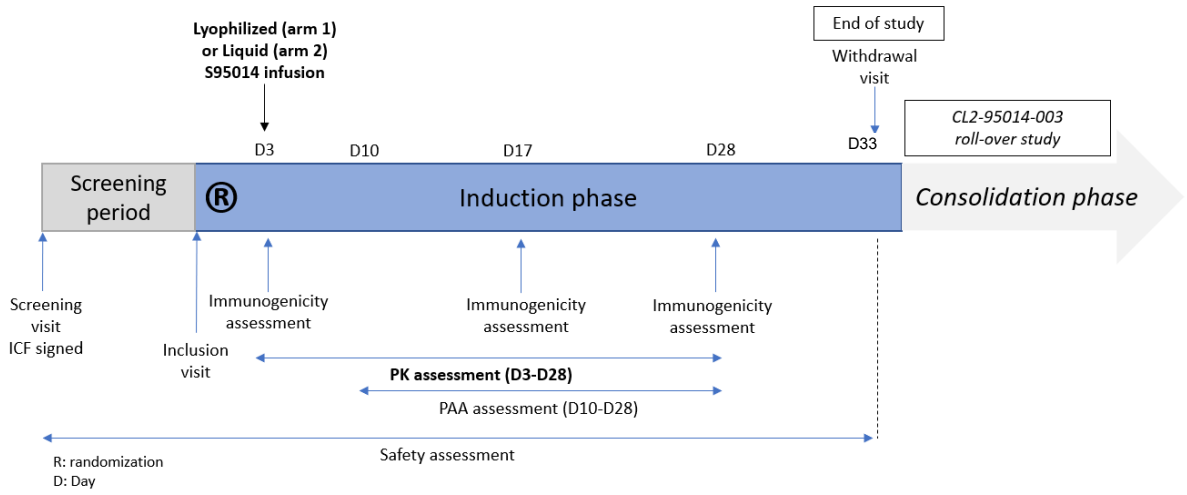
Methodology:

This was a multicenter, randomized, open-label, phase II clinical study conducted in 7 sites in Russia that compared the PK and safety of LYO and LIQ pegaspargase (Oncaspar®, S95014) formulations in 2 parallel groups of newly diagnosed, untreated pediatric patients (1 – 17 years old) with ALL.

Patients were randomly assigned (1:1) to either LYO S95014 or LIQ S95014 administered intravenously at the dose of 2,500 U/m² at Day 3, in combination with other backbone chemotherapy agents as per the Childhood ALL Protocol Moscow-Berlin 2015 (ALL-MB 2015) and local practice.

The study plan is shown below:



The study was divided into two periods:

- Screening period (Day -14 to Day -1), to check patients eligibility.
- Induction phase (Day 0 to Day 33):
  - Inclusion visit (Day 0), to confirm patients eligibility;
  - Randomization to one of the two treatment groups LYO S95014 or LIQ S95014 followed by IMP administration on Day 3;
  - Withdrawal/End-of-study visit, at least 30 days after S95014 infusion (*i.e.* Day 33) and before starting the consolidation phase. At study end, patients were proposed to enter into a roll-over study (CL2-95014-003) for the consolidation phase using LYO S95014 in combination with backbone regimen as per ALL-MB 2015.

Eleven blood samples were taken for PAA analysis during the study:

- Pre-dose and just after the end of infusion;
- At the following timepoints after the end of infusion: 4 hours, 24 hours, 48 hours, 120 hours (5 days), 168 hours (7 days)*, 216 hours (9 days), 336 hours (14 days)*, 432 hours (18 days)* and 600 hours (25 days)*.

All 11 timepoints were used for PK assessments. Four timepoints (identified by an asterisk) were used for assessing achievement of PAA ≥ 100 mU/mL.

Other assessments included:

- Immunogenicity: anti-S95014 and anti-polyethylene glycol (PEG) measured by enzyme-linked immunosorbent assay (ELISA) at pre-dose, 14 and 25 days post-dose.
- Standard safety assessments throughout the study (see Endpoints for details).

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Number of patients:

Planned: 90 included / 78 evaluable for PK (39 per group).

Actual: 89 included (44 [LYO] and 45 [LIQ]) / 81 evaluable for PK (41 [LYO] and 40 [LIQ]).

Diagnosis and main criteria for inclusion and exclusion:

Main inclusion criteria were male or female patients aged ≥ 1 to < 18 years, with a cytologically confirmed and documented newly diagnosed ALL according to National Comprehensive Cancer Network (NCCN) guidelines 2020 (excluding B-cell Burkitt ALL), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2.

Main exclusion criteria were inadequate hepatic function (total bilirubin > 1.5 times upper limit of normal [ULN], transaminases > 5 x ULN) and inadequate renal function (serum creatinine > 1.5 x ULN).

Test drug:

Investigational Medicinal Product (IMP): pegaspargase (S95014), LYO formulation

Unit Dosage: 3,750 U per 5 mL vial after reconstitution with 5.2 mL of sterile water for injection

Dosage frequency and mode of administration: 1 hour IV infusion on Day 3 at 2,500 U/m^2 of body surface area (BSA).

Batch numbers: L0078610, L0079399, L0079872

Comparator (Reference product):

IMP: pegaspargase (S95014), LIQ formulation

Unit Dosage: 3750 U per 5 mL vial

Dosage frequency and mode of administration: 1 hour IV infusion on Day 3 at 2,500 U/m^2 of BSA.

Batch numbers: L0079105, L0079284, L0079429, L0079699, L0080066, L0080087, L0080382, L0080759, L0080981

Duration of treatment:

Screening period: up to 14 days.

Treatment period: Induction phase of approximately 30 days during which patients received a single administration of the IMP (Day 3) and backbone chemotherapy regimen as per ALL-MB 2015.

Endpoints:

Primary endpoint

***PK parameters*:** Maximum observed PAA (C_{max}) (mU/mL) and Area Under the PAA-time Curve (AUC) (mU*day/mL), calculated by non-compartmental analysis (NCA) approach based on observed PAA time profiles.

Secondary endpoints:

Additional PK parameters: lowest observed PAA 14 days post-dose (C_{Day14}); time to maximum PAA (T_{max}); last observed PAA (C_{last}); time to last observed PAA (T_{last}) and terminal half-life ($T_{1/2}$).

Achievement of PAA threshold ≥ 100 mU/mL: on Day 10, Day 17, Day 21 and Day 28 (i.e. 7, 14, 18 and 25 days post dose).

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Immunogenicity measurements: Anti-S95014 and anti-PEG antibodies at pre-dose, Day 17 and Day 28 (i.e. 14 and 25 days post dose).

Safety assessments:

- Adverse events (AEs), treatment emergent AEs (TEAEs).
- AEs of special interest (AEOSI) defined as follows: Grade ≥ 3 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase, or Grade ≥ 3 hyperbilirubinemia; Grade ≥ 3 hemorrhage or Grade ≥ 3 thromboembolic events; Grade ≥ 3 pancreatitis; and Grade ≥ 3 hypersensitivity.
- Physical examinations and ECOG PS.
- Laboratory abnormalities assessment including hematology, blood biochemistry, urinalysis, and coagulation parameters.
- Vital signs.
- Report of any change or addition of a new concomitant treatment.

***Efficacy*:**

Not applicable

Statistical methods:

Analysis Sets:

Full Analysis Set (FAS): All randomized patients (patients were classified according to treatment assigned at randomization).

Safety Analysis Set (SAS): All patients who had received at least one dose of IMP (patients were classified according to the actual treatment received).

Pharmacokinetic Analysis Set (PKAS): All patients who had received at least one dose of IMP and were evaluable for PK analysis. Evaluable patients were those who had enough samples collected and no deviations that could affect the interpretation of PK results. Exclusion of patients from the PKAS was determined on a case-by-case basis. The anti-drug antibody (ADA)-positive patients were a priori included in the PKAS since no impact was identified based on the population PK model.

Immunogenicity Analysis Set (IAS): All patients who had received at least one dose of IMP and had at least one post-dose sample evaluable for immunogenicity testing.

PK analysis:

PK parameters were derived using Phoenix® WinNonlin® 8.3 (Certara) by NCA approach using actual elapsed time from the start of the respective dose administration and calculated for each patient. PK parameters included: AUC from time 0 to the time of the last observed non-zero PAA ($AUC_{0\text{-}Tlast}$); AUC from time 0 extrapolated to infinity (AUC_{inf}); percent of AUC_{inf} extrapolated ($AUC_{\%ext}$); C_{max}; T_{max}; $C_{day\ 14}$; C_{last}; T_{last}; and $T_{1/2}$.

A statistical analysis was used to compare the primary endpoints using an analysis of variance (ANOVA) model on the natural logarithm transformed PK parameters (C_{max}, AUC_{inf} and $AUC_{0\text{-}Tlast}$) for the LYO formulation (test) versus the LIQ formulation (reference) using the PKAS. The two one-sided tests procedures were performed on the geometric mean ratio (GMR) between test (LYO S95014) and reference (LIQ S95014) treatments. The 90% confidence interval (CI) was obtained by exponentiation of the upper and lower 90% confidence limits for the difference of logarithm means. PK comparability between the test treatment and the reference treatment was concluded if the 90% CI for AUC and C_{max} GMR was within the [80.00%; 125.00%] range. An additional comparison was performed on C_{day14} for informational purposes.

Descriptive statistics of the PK parameters were summarized by treatment (arithmetic mean, standard deviation [SD], geometric mean, geometric coefficient of variation [CV], median, min, max).

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Additional summaries of PK parameters were presented by positive or negative anti-S95014 antibody status at baseline. Individual and mean PK parameters were presented.

Descriptive statistics of PAA (arithmetic mean, geometric mean, % coefficient of variation [%CV], SD, median, min, max) were also calculated and tabulated per nominal sampling time by treatment group. PAA over time was plotted in semilogarithmic and linear formats as mean ± SD and as median (Q1, Q3), using the nominal timepoints.

PAA threshold analysis:

The number and proportion of patients having achieved a PAA of ≥ 100 mU/mL at Day 10, Day 17, Day 21 and Day 28 (i.e. 7, 14, 18 and 25 days post dose) were summarized by treatment along with a 2-sided 95% Clopper-Pearson CI. Analysis was carried out in the SAS.

Immunogenicity analysis:

The number and proportion of patients having anti-S95014 ± anti-PEG antibodies at Day 17 and Day 28 (i.e 14 and 25 days post dose) were summarized by treatment.

Safety analysis:

Safety was summarized using descriptive statistics.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 89 patients were included in the study and randomly assigned (1:1) to:

- S95014 LYO group: 44 patients;
- S95014 LIQ group: 45 patients.

Four (4.5%) patients overall, all randomized in the LIQ group, were prematurely withdrawn from the study: 2 patients had a fatal AE, 1 patient was included with a deviation to an inclusion criterion and was withdrawn before receiving the IMP (the patient had B-cell Burkitt ALL), and 1 patient had an allergic reaction after starting the IMP infusion and was withdrawn by the investigator's decision.

Disposition of patients in the FAS and counts of patients in each analysis set

	S95014 Lyophilizate (N = 44)	**S95014 Liquid (N = 45)**	**Overall (N =89)**
Included	**44**	**45**	**89**
Withdrawn due to	**-**	**4 (8.9)**	**4 (4.5)**
adverse event(1)	-	2 (4.4)	2 (2.2)
protocol deviation(2)	-	1 (2.2)	1 (1.1)
physician decision(3)	-	1 (2.2)	1 (1.1)
Completed	**44 (100.0)**	**41 (91.1)**	**85 (95.5)**
Full Analysis Set (FAS)	**44**	**45**	**89**
Safety Analysis Set(4) (SAS)	**43**	**45**	**88**
Pharmacokinetic Analysis Set (PKAS)	**41**	**40**	**81**
Immunogenicity Analysis Set(4) (IAS)	**43**	**43**	**86**

Results are shown as count of patients (%).
(1) AEs with fatal outcomes.
(2) One patient wrongly included with B-cell Burkitt ALL; withdrawn before receiving any IMP.
(3) One patient had an allergic reaction after starting the infusion with the IMP.
(4) One patient randomized in the LYO group received the LIQ formulation in error and was classified according to the treatment actually received.

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In all, 23 (25.8%) patients of the FAS had a protocol deviation before or at inclusion (22.7% in the LYO group *versus* 28.9% in the LIQ group), mostly a missing blood biochemistry parameter.

Protocol deviations after inclusion occurred in 28 (31.5%) patients of the FAS (25.0% in the LYO group *versus* 37.8% in the LIQ group) and concerned mostly missing blood biochemistry assessments. Six (6.7%) patients had deviations that could have compromised the interpretation of the primary PK endpoint, mostly missing PK timepoints. Of these 6 patients, 5 (2 in the LYO group and 3 in the LIQ group) were excluded from the PKAS. Another noteworthy deviation occurred in 1 patient randomized to the LYO group who received the liquid formulation in error. The received formulation was expired leading to an exclusion from the PKAS. This patient was analysed according to the treatment actually received in the safety and immunogenicity (ADA) analyses.

BASELINE CHARACTERISTICS

In the Safety Analysis Set, mean age (± SD) was 6.1 ± 3.96 years overall (min - max: 1 – 17 years old, in line with the inclusion criteria). Of note, patients of the LYO group were slightly older than those of the LIQ group: mean of 6.9 years *versus* 5.4 years, respectively. This was due to a higher proportion of patients aged 10 years and older in the LYO group (13 patients, 30.2%) than in the LIQ group (7 patients, 15.6%). Consistent with this slight age difference observed between groups, mean BMI and BSA were slightly higher in the LYO group *versus* the LIQ group (BMI: 17.2 kg/m^2 *versus* 15.8 kg/m^2; BSA: 1.0 m^2 *versus* 0.8 m^2, respectively). Males were predominant in the LYO group (26 patients, 60.5%) but not in the LIQ group (20 patients, 44.4%). The majority of patients were of Caucasian origin in both study groups (84 patients, 95.5% overall). Most patients had a B-cell type ALL (LYO group: 93.0% ; LIQ group: 93.3%) and an ECOG PS of 1 at baseline (LYO group: 55.8%; LIQ group: 68.9%). Baseline clinical laboratory values were consistent with ALL, with no clinically relevant between-arm differences for most parameters. Ten (11.6%) patients were positive for ADAs at baseline, with an identical frequency between treatment groups (5 [11.6%] patients in each group). No clinically relevant between-group differences were observed for the other baseline characteristics, , medical and surgical history, and previous treatments.

Baseline characteristics in the PKAS were similar to those described above in the Safety Analysis Set.

EXTENT OF EXPOSURE

All 88 patients received the per-protocol dose of 2,500 U/m² of S95014 (relative dose intensity [RDI] of 1.0), except 1 patient in the lyo. group who received a dose of 2569 U/m^2 (RDI of 1.028). Of note, 3 patients (1 in the LYO group and 2 in the LIQ group) had their infusion time deviating by ±10% from the nominal infusion time of 1 hour (all 3 patients had their infusion interrupted due to an allergic reaction).

PHARMACOKINETIC RESULTS

No difference was observed in plasma asparaginase activity (PAA) peak (C_{max}) and total exposures (AUC_{inf}) following administration of the lyophilized (test) formulation compared to the liquid (reference) formulation. The 90% confidence interval of the geometric mean ratio (GMR) was completely contained within the [80.00%-125.00%] interval for C_{max} and AUC_{inf}

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Geometric Mean Ratios of Pharmacokinetic Parameters - Pharmacokinetic Analysis Set (N=81)

PK parameter		S95014 lyophilizate (N=41)	S95014 liquid (N=40)
C_{max} (mU/mL)	n	41	40
	Geometric mean	1563.115	1672.136
	Geometric mean ratio	93.5%	
	(90% CI)	(82.9%, 105.5%)	
AUC_{inf} (mU*day/mL)	n	41	39
	Geometric mean	362028.656	352248.907
	Geometric mean ratio	102.8%	
	(90% CI)	(91.4%,115.6%)	
$AUC_{0\text{-}Tlast}$ (mU*day/mL)	n	41	40
	Geometric mean	341906.017	295025.182
	Geometric mean ratio	115.9%	
	(90% CI)	(90.2%,148.9%)	
C_{day14} (mU/mL)	n	41	39
	Geometric mean	496.599	408.655
	Geometric mean ratio	121.5%	
	(90% CI)	(98.7%,149.6%)	

In the fixed effects model, the dependent variable is log transformed PK parameters, the fixed effect is treatment arm.
Source: Table 14.2.2

A 16% increase in PAA exposure ($AUC_{0\text{-}tlast}$) and a 22% increase in C_{day14} was observed following administration of the lyophilized (test) formulation compared to the liquid (reference) formulation. The 90% CI for the GMR was partially contained within the [80.00%-125.00%] interval. This increase is not expected to impact the efficacy and the safety of S95014.

These results support the conclusion that Oncaspar IV 2,500 U/m^2 pharmacokinetic exposure does not depend on formulation.

PLASMA ASPARAGINASE ACTIVITY

Nearly all patients of the Safety Analysis Set achieved a PAA level ≥ 100 mU/mL between 7 and 18 days after the IMP infusion (% of patients ranging from 90.7% to 100% in each treatment group across study visits).

This proportion was markedly reduced at 25 days after infusion in both treatment groups but remained higher in the LYO group *versus* the LIQ group: 18 patients (42.9%) *versus* 6 patients (14.0%) achieved a PAA level of 100 mU/mL or more in the LYO group and the LIQ group, respectively.

IMMUNOGENICITY RESULTS (ADAs)

Overall, 10 out of 86 patients (11.6%) were positive for ADAs (anti-S95014) at baseline with an identical frequency between treatments groups (5 in each group). 6 out of the 10 patients were also positive to anti-PEG antibodies: 2/43 patients (4.7%) following the administration of the lyophilizate formulation and 4/43 patients (9.3%) following the administration of the liquid formulation.

Upon treatment, seroconversion was observed in a total of 5 patients out of 86 that included 3/43 patients (7%) following the administration of liquid formulation and in 2/43 patients (4.7%) following the administration of lyophilizate formulation. The development of ADA did not translate into an impact of PK properties, safety or efficacy.

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SAFETY RESULTS

Adverse events

Summary of treatment emergent adverse events in the Safety Analysis Set

	S95014 Lyophilizate (N=43)		S95014 Liquid (N=45)		Overall (N= 88)	
	n	**%**	**n**	**%**	**n**	**%**
Any TEAEs	43	100.0	45	100.0	88	100.0
Grade 3/4 TEAEs	42	97.7	43	95.6	85	96.6
TEAEs suspected to be IMP related	38	88.4	41	91.1	79	89.8
Serious TEAEs	19	44.2	18	40.0	37	42.0
Treatment emergent AEOSI	11	25.6	9	20.0	20	22.7
Serious TEAEs suspected to be IMP related	8	18.6	4	8.9	12	13.6
Treatment emergent serious AEOSI	5	11.6	0	0.0	5	5.7

n: Number of patients who had at least one AE in each AE type. Percentages are based on N.
Treatment emergent SAEs or TEAEs related to IMP include sponsor upgrade.

All % below are proportion of patients in the Safety Analysis Set, except otherwise indicated.

All 88 (100%) patients of the Safety Analysis Set had at least an AE during the study, for a total of 874 events, including 796 (91.1%) that were emergent under treatment. The number of total emergent events was 416 (52.3%) in the LYO group *versus* 380 (47.7%) in the LIQ group.

Emergent adverse events

- The most frequently affected SOCs in both treatment groups were investigations 84/88 (95.5%) and blood and lymphatic systemic disorders 63/88 (71.6%). Some SOCs showed a trend for an imbalance between treatment groups, with no consistent pattern towards one group in particular
- The reported TEAEs were consistent with the known adverse reactions of S95014 and with ALL. The most common PTs in the treatment groups were blood fibrinogen decreased (73 [83.0%]), antithrombin III decreased (64 [72.7%]) and lymphocyte count decreased (59 [67.0%]). Some PTs showed a trend for an imbalance between treatment groups, with no consistent pattern towards one group in particular.
- Most TEAEs were of Grade 2 (31.5% of total TEAEs) or of Grade 3 (30.5% of total TEAEs), with a similar distribution in severity between treatment groups. Severe and life-threatening (Grade 3/4) TEAEs were reported for 85 (96.6%) patients overall, with a similar frequency in the LYO group *versus* the LIQ group: 42 (97.7%) versus 43 (95.6%), respectively.
- Most patients (79 [89.8%]) reported at least one TEAE considered related to the IMPs, with a similar frequency in the LYO group *versus* the LIQ group. The most common IMPs-related TEAEs were blood fibrinogen decreased (70.5%), antithrombin III decreased (67.0%) and lymphocyte count decreased (48.9%).
- A total of 4 patients (1 in the LYO group and 3 in the LIQ group) had a TEAE leading to an interruption of IMP infusion, mostly due to allergic reactions.

SAFETY RESULTS (continued)

Emergent serious adverse events

- Emergent SAEs were reported in 37 (42.0%) patients overall, with a comparable frequency between treatments (19 patients [44.2%] in the LYO group *versus* 18 [40.0%] patients in the LIQ group). The three most frequently reported serious PTs were febrile neutropenia (8 patients [9.1%]), leukopenia (8 patients [9.1%]), and lymphocyte count decreased (7 patients, 8.0%), with a comparable frequency between treatment groups. Of note, there was a trend for a higher frequency of serious infections and infestation in the LYO group *versus* the LIQ group (9 patients [20.9%] *versus* 2 patients [4.4%] respectively), with no particular predominant PT.
- Three (3.4%) patients had TEAEs with fatal outcomes (1 patient in the LYO group and 2 patients in the LIQ group). These were either sepsis and/or multiple organ dysfunction syndrome, none of them considered as related to the IMPs.
- Emergent SAEs considered related to the IMPs were reported at a higher frequency in the LYO group (8 patients, 18.6%) than in the LIQ group (4 patients, 8.9%). This imbalance was mostly driven by the SOC gastrointestinal disorders (4 patients [9.3%]) in the LYO group including 2 cases of edematous pancreatitis and 1 of pancreatitis acute and 1 case of neutropenic colitis *versus* 1 case of neutropenic colitis in the LIQ group.

Emergent adverse events of special interest

- Emergent AEOSIs were reported in 20 (22.7%) patients overall, with a comparable frequency in the LYO group *versus* the LIQ group: 11 (25.6%) patients versus 9 (20.0%) patients, respectively. The most frequently reported PTs were Grade ≥ 3 ALT increase in 14 (15.9%) patients overall, with a similar frequency in the LYO group *versus* the LIQ group. All other PTs were reported in 2 patients at most in each treatment group with no relevant differences between treatment groups. Most emergent AEOSIs (87.5% of total events) were rated Grade 3, with a similar distribution in severity between treatment groups. no AEOSI had a fatal outcome.
- Emergent serious AEOSIs were reported in 5 patients overall, all in the LYO group (11.6%), for a total of 10 events, with no predominant PT. Of these 10 events, 3 were related to backbone therapy (1 event each of hyperbilirubinemia, hepatosplenomegaly, and hepatotoxicity), 2 events of edematous pancreatitis were related to both IMP and backbone therapy, whereas the 5 remaining events were not considered as treatment related.

Clinical laboratories

- *Biochemistry*: No consistent trend for a clinically relevant between-arm difference over time was noted for any of the blood and urine parameters despite a trend for a higher proportion of patients with abnormal value observed in the lyo group versus the LIQ group. Most frequently reported emergent Grade ≥ 3 values concerned ALT (21 patients, 23.9%), potassium (14 patients, 15.9%), and GGT (12 patients, 13.6%).
- *Hematology*: There was a trend for a lower mean and median counts of leukocytes, neutrophils, lymphocytes and platelets in the LYO group *versus* the LIQ group across post-baseline visits. Most frequently reported emergent Grade ≥ 3 values concerned lymphocyte counts (63 patients, 71.6%) and leukocyte counts (84 patients, 95.4%).
- *Blood coagulation*: Low antithrombin activity was more frequently reported in the LYO group *versus* the LIQ group at post-baseline visits up to Day 24: 81.4% *versus* 62.8% at Day 10, 85.4% *versus* 58.1% at Day 17, and 63.4% *versus* 40.5% at Day 24. The most frequently reported emergent Grade ≥ 3 values concerned fibrinogen (34.1% overall) with a similar frequency between treatment groups.

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SAFETY RESULTS (continued)

Vital signs and ECOG PS

- *Vital signs*: No clinically significant changes were observed for systolic and diastolic blood pressure, heart rate and body temperature from baseline and between treatment groups. A small between-arm difference was observed in the mean change from baseline in diastolic blood pressure (DBP) and heart rate (HR) but considered as not clinically meaningful due to the high variability of the measure.
- *ECOG PS*: There was a general improvement in ECOG PS at the last visit compared to baseline in both treatment groups: the proportion of patients with a PS of 0 or 1 at baseline increased from 80.7% at baseline to 90.6% at the last visit (LYO group: 76.7% to 88.4%; LIQ group: 84.4% to 92.9% at baseline and last visit, respectively).

CONCLUSION

No difference was observed in PAA peak (C_{max}) and total PAA exposures (AUC_{inf}) following administration of the LYO (test) formulation compared to the LIQ (reference) formulation.

A 16% increase in PAA exposure ($AUC_{0\text{-}tlast}$) and a 22% increase in C_{day14} was observed following administration of the LYO (test) formulation compared to the LIQ (reference) formulation. This increase is not expected to impact efficacy or safety of the drug product.

Nearly all patients achieved a PAA level ≥ 100 mU/mL up to 18 days post-infusion with both formulations.

No clinically significant difference on the safety profile was observed between the two formulations. No new safety concerns for either formulation was detected. The safety profile is consistent with findings from previous studies.

Therefore, these results support the conclusion that the PK exposure of Oncaspar® after IV administration at the dose of 2,500 U/m² does not depend on formulation.

Date of the report: 28 October 2022

Version of the report: Final Version