I.R.I.S.

Institut de Recherches Internationales Servier

Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	A multicentre, 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 Paediatric Patients with Newly-Diagnosed Acute Lymphoblastic Leukemia (ALL)
Study brief title	Pharmacokinetics comparability study of Liquid and Lyophilized pegaspargase (S95014) formulations in ALL
Study public title	A study comparing the blood levels of both pegaspargase (S95014) formulations (liquid vs lyophilized) in the Treatment of Paediatric Patients with Acute Lymphoblastic Leukemia (ALL)
Test drug code	S95014 / pegaspargase / Oncaspar®
Indication	Acute Lymphoblastic Leukemia
Development phase	II
Protocol code	CL2-95014-002
EudraCT Number	2020-004894-29
Universal Trial Number	Not applicable
Other register number (ISRCTN, CT. gov…)	NCT04954326
Investigational New Drug Application Number	152433
Sponsor	I.R.I.S.
International Coordinator	Pr Alexander Karachunskiy Institute of Oncology, Radiology and Nuclear Medicine Dmitry Rogachev National Medical Research Center Moscow, Russia
Date of the document	2 December 2020
Version of the document	Final version

Version No	Final version date	Countries concerned
2.0	2 Dec 2020	INT

CONFIDENTIAL

FOLLOW-UP OF VERSIONS

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
1.0	NA	22 Oct 2020	ALL	Not Applicable
2.0	NA	2 Dec 2020	ALL	Modifications were provided to the study protocol following FDA's non-hold comments: - Clarification about the collection of PK and PAA samples - Addition of an immunogenicity timepoint 14 days post-dose (Day 17) - Clarification about the sample size calculation - Addition of C_{trough} 14 days post-dose as a PK secondary endpoint - Deletion of a specific dosing regimen of 82.5 U/kg for patients with low BSA - Additional minor changes

SYNOPSIS

Name of the sponsor:
I.R.I.S.

Name of Finished Product:
Lyophilized pegaspargase
Liquid pegaspargase

Name of Active Ingredient:
Pegaspargase
S95014
Oncaspar®

Title of study: A multicentre, 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 Paediatric Patients with Newly-Diagnosed Acute Lymphoblastic Leukemia (ALL)

Study Brief Title: Pharmacokinetics comparability study of Liquid and Lyophilized pegaspargase (S95014) formulations in ALL

Study Public Title*:* A study comparing the blood levels of both pegaspargase (S95014) formulations (liquid vs lyophilized) in the Treatment of Paediatric Patients with Acute Lymphoblastic Leukemia (ALL)

Protocol No.: CL2-95014-002

Coordinator, Investigators
National coordinator and investigators: listed in a separate document

Study centre(s):
6-10 centres in Russia

Study period:

- Study duration for the participant: approximately 1.5 month
- Study initiation date (planned date of first visit first participant): Q1/Q2 2021
- Study completion date (planned date of last visit last participant): Q2 2022

Study development phase: II

Objective(s):

Primary objective:

To compare the pharmacokinetics (PK) of both lyophilized and liquid S95014 formulations during the induction phase after a single IV dose in newly diagnosed paediatric patients with ALL

Secondary objectives:

- To describe the PK of S95014 after administration of either lyophilized or liquid formulation
- To evaluate the achievement of plasma asparaginase activity (PAA) of ≥0.1 U/mL after the administration of either lyophilized or liquid S95014
- To assess the immunogenicity of both lyophilized and liquid S95014 formulations
- To evaluate the safety profile through the occurrence of TEAEs including serious adverse events (SAEs), regardless of causality and severity

Methodology:

This is a multicentre, randomized, open-label, phase II clinical study comparing the pharmacokinetics of lyophilized and liquid Pegaspargase (Oncaspar®, S95014) formulations in the treatment of newly diagnosed, untreated pediatric patients with ALL.

Written informed consent and assent (when appropriate) will be obtained from each patient and/or his/her parent(s)/legal representative before initiation of study procedures. Patients will undergo screening after giving informed consent and will be included once all eligibility requirements for the study have been met.
Baseline evaluations and risk stratification will be performed in compliance with the current ALL-MB 2015

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Name of Finished Product: Lyophilized pegaspargase Liquid pegaspargase
Name of Active Ingredient: Pegaspargase S95014 Oncaspar®
protocol. Each patient will be randomly assigned (1:1) to receive either lyophilized (arm 1) or liquid (arm 2) S95014 intravenously over 1-hour at the dose of 2500 U/m² at Day 3 during the induction phase. Backbone chemotherapy agents will be administered as per ALL-MB 2015 protocol. The study duration will be approximately 1.5 month, including the screening (14 days) and the treatment period consisting of the induction phase (approximately 30 days). After completing the induction phase, patient will be discontinued from the study and, provided that the inclusion/non-inclusion criteria are fulfilled, will be proposed to enter a roll-over study for the consolidation phase, in compliance with ALL-MB 2015 protocol. Eleven (11) sodium heparinised plasma for pharmacokinetic (serial PK samples) will be obtained, as follows: pre-dose, just after the end of infusion (on Day 3), 4 hours after the end of infusion (on Day 3), 24 hours after the end of infusion (on Day 4), 48 hours after the end of infusion (on Day 5), 120 hours (i.e. 5 days) after the end of infusion (on Day 8), 168 hours (i.e. 7 days) after the end of infusion (on Day 10), 216 hours (i.e. 9 days) after the end of infusion (on Day 12), 336 hours (i.e. 14 days) after the end of infusion (on Day 17), 432 hours (i.e. 18 days) after the end of infusion (on Day 21) and 600 hours (i.e. 25 days) after the end of infusion (on Day 28). Four (4) sodium heparinised plasma for asparaginase activity assessment will be obtained 7, 14, 18 and 25 days after the administration of liquid or lyophilized S95014 (on Day 10, Day 17, Day 21 and Day 28). Samples collected for PAA assessment will be the same as for PK analysis to avoid duplicating sample collection. Three (3) sodium heparinised plasma for assessment of anti S95014 and anti-PEG antibodies will be obtained at pre-dose, 14 and 25 days after the infusion (i.e. on Day 17 and Day 28). All adverse events regardless of grade or causality will be collected after the informed consent is signed and during the entire treatment period.
Number of included participants: Approximately 88 patients will be included to ensure 78 evaluable patients
Diagnosis and main criteria for inclusion: Screening criteria - Patients aged 1 to < 18 years - Patients with cytologically confirmed and documented newly diagnosed ALL according to NCCN guidelines 2020 (see Appendix 2), excluding B-cell Burkitt ALL - Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2 (see Appendix 3) - Highly effective contraception method - Signed informed consent and assent, when appropriate Non-screening criteria: - Unlikely to cooperate in the study - Pregnant and lactating women - Participation in another interventional study at the same time; participation in non-interventional registries or epidemiological studies is allowed - Participant already enrolled in the study (informed consent signed)

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Name of Finished Product:
Lyophilized pegaspargase
Liquid pegaspargase

Name of Active Ingredient:
Pegaspargase
S95014
Oncaspar®

- Prior treatment with chemotherapy or radiotherapy (except steroids and intrathecal therapy)
- Prior surgery or bone marrow transplant related to the studied disease
- Down Syndrome
- Psychiatric illness/social situation that would limit compliance with study requirements
- Known history of pancreatitis
- Known history of significant liver disease
- Known carriers of HIV antibodies
- Significant laboratory abnormality likely to jeopardize the patients' safety or to interfere with the conduct of the study, in the investigator's opinion
- Pre-existing known coagulopathy (e.g. haemophilia and known protein S deficiency)
- History of previous or concurrent malignancy
- History of sensitivity to polyethylene glycol (PEG) or PEG-based drugs
- Severe or uncontrolled active acute or chronic infection
- Uncontrolled intercurrent illness including life-threatening acute tumor lysis syndrome (e.g. with renal failure), symptomatic congestive heart failure, cardiac arrhythmia

Inclusion criteria:
Screening criteria must still be fulfilled at the time of the inclusion visit

Non-inclusion criteria:
Non-screening criteria must still be fulfilled at the time of the inclusion visit

- Women of childbearing potential tested positive in a serum pregnancy test within 7 days prior to the treatment period
- Inadequate hepatic function (bilirubin > 1.5 times upper limit of normal (ULN), transaminases > 5 x ULN)
- Inadequate renal function defined as serum creatinine > 1.5 x ULN

Test drug:
S95014 liquid (reference drug) and S95014 lyophilizate (test drug) are both IMPs

- Arm 1: lyophilized S95014 reconstituted will provide 5 mL of extractable volume with the concentration of 750 U/mL. The vial of lyophilized powder (3.750 U/vial) is reconstituted with 5.2 mL of SWFI to obtain a 750 U/mL solution for single use.
- Arm 2: liquid S95014 is provided as 3.750 U per 5 mL solution in a single use vial to obtain a 750 U/mL solution for single use.

S95014 (either liquid or lyophilized) will be intravenously administered over 1 hour at the dose of 2500 U/m^2 at Day 3 of the induction phase. Patients will receive other backbone chemotherapy agents as per ALL-MB 2015 protocol.

Comparator: Liquid S95014 (reference drug)

Duration of treatment:
Screening period: up to 14 days
Active treatment period: approximately 30 days

Criteria for evaluation:
Primary endpoint:

Pharmacokinetics measurement:

The following PK parameters will be determined: Area Under the Concentration-Time curve (AUC);

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Name of Active Ingredient: Pegaspargase S95014 Oncaspar®

maximum observed plasma asparaginase activity (C_{max}).
The above parameters will be calculated using non-compartmental analysis (NCA) approach based on observed plasma asparaginase activity (PAA) time profiles. These will be calculated for each patient and the corresponding descriptive statistics of PK parameters will be tabulated (arithmetic mean, SD, geometric mean, geometric CV, median, min, max).

Statistical analysis of the primary endpoint (AUC and C_{max}) will consist in an analysis of variance (ANOVA) and a 90% confidence interval for the ratios of the geometric means of PAA (after administration of lyophilized formulation)/ PAA (after administration of liquid formulation) will be calculated for C_{max} and AUC using respective residual variances.
The acceptance limits of the confidence intervals for geometric means ratios of asparaginase activity will be those defined in guidelines, i.e. [80.00%; 125.00%], to conclude that there is a comparability between one IV administration of lyophilized formulation versus one IV administration of liquid formulation

Secondary endpoints:

Pharmacokinetics measurements:
Additional PK parameters from the ones defined as primary endpoint (e.g. C_{trough} at 14 days post-dose, T_{max}, $T_{1/2}$) will be assessed.
A statistical analysis will be performed on $C_{trough,\ day\ 14}$ with an analysis of variance (ANOVA) and a 90% confidence interval for the ratios of the geometric mean for this parameter.

Activity measurement:
Plasma Asparaginase Activity (PAA) of ≥ 0.1 U/mL 7, 14, 18 and 25 days (i.e. Day 10, Day 17, Day 21 and Day 28) after the administration of either liquid or lyophilized S95014.
Observed individual PAA level 7, 14, 18 and 25 days after administration of either liquid or lyophilized S95014 will be tabulated together with descriptive statistics (Arithmetic mean, SD, geometric mean, geometric CV, median, min, max). The number and proportion of patients achieving a PAA of ≥ 0.1 U/mL 7, 14, 18 and 25 days after the administration of either liquid or lyophilized S95014 will be summarized.

Immunogenicity measurements:
Anti S95014 and anti-PEG antibodies will be assessed at pre-dose, 14 and 25 days after the S95014 infusion (i.e. Day 17 and Day 28). This evaluation will be based on qualitative enzyme-linked immunosorbent assay (ELISA) using S95014 as coating antigen. All positive samples will be further confirmed by competitive ELISA for the presence of binding antibodies against S95014. Samples, when confirmed positive, will then be assayed for the antibodies against PEG. The number and proportion of patients having anti S95014 ± anti-PEG antibodies 14 and 25 days (Day 17 and Day 28) after the administration of either liquid or lyophilized S95014 will be summarized.

Safety measurement:
Safety assessments will be performed and reported throughout the study. This will include:

- adverse events (AEs), treatment emergent adverse events (TEAEs), adverse events of special interest (AESI) assessments
- physical examinations, performance status
- laboratory abnormalities assessment including haematology, blood biochemistry, urinalysis, coagulation parameters
- vital signs measurements

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Name of Finished Product: Lyophilized pegaspargase Liquid pegaspargase
Name of Active Ingredient: Pegaspargase S95014 Oncaspar®
- Recording of any change or addition of a new concomitant treatment Adverse events will be collected regardless of grade or IMP relationship and will be graded according to current NCI CTCAE criteria 5.0 Safety analysis: descriptive summaries of demographic and baseline characteristics with a description of patient disposition and listing of medical history will be provided. The number and percentage of patients with adverse events will be tabulated by system organ class and preferred term. Determination of sample size: This study is a two-arm parallel 1:1 randomized trial to evaluate the PK comparability between liquid and lyophilized S95014 formulations. For both AUC and C_{max}, the coefficient of variation (CoV) of 0.30 is assumed based on the estimation of CoV for liquid S95014 from a previous study (Angiolillo, 2014). Assuming a CoV of 0.30 and a true geometric mean ratio (GMR) of 100%, a total of 78 evaluable subjects (39 subjects per arm) will provide approximately 90% power to establish the PK comparability. Assuming that 10% of the included patients will not be evaluable (e.g. missing PK timepoint etc.), 88 subjects are expected to be included to allow 78 evaluable patients.
Data Monitoring Committee: Not applicable

Contractual signatories	
I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice (GCP) and the applicable regulatory requirements. ***COORDINATOR/INVESTIGATOR**:*	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
HEAD OF LATE STAGE AND LIFE CYCLE MANAGEMENT DEPARTMENT:	
NAME	[redacted]
DATE	7 Dec 2020
SIGNATURE	[redacted]

Other sponsor's signatories	
BIOSTATISTICS HEAD:	
NAME	[redacted]
DATE	12/2/2020
SIGNATURE	[redacted]

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List of abbreviations

ADA	:	Anti-Drug Antibodies
ADL	:	Activities of Daily Living
AE	:	Adverse Event
AEOSI	:	Adverse Event Of Special Interest
ALL	:	Acute Lymphoblastic Leukemia
ALP	:	Alkaline Phosphatase
ALT	:	ALanine aminoTransferase
ANOVA	:	Analysis of Variance
APTT	:	Activated Partial Thromboplastin Time
AST	:	ASpartate aminoTransferase
AUC	:	Area Under the Curve
BFM	:	Berlin-Frankfurt-Munster
BMI	:	Body Mass Index
BP	:	Blood Pressure
bpm	:	beats per minute (heart rate unit)
BSA	:	Body Surface Area
BUN	:	Blood Urea Nitrogen
CBI	:	Central Business Intelligence
CHMP	:	Committee for Medical Products for Human Use
CI	:	Confidence Interval
cm	:	centimetre
Cmax	:	maximum Concentration
$C_{trough, day 14}$	:	Lowest concentration reached by a drug 14 days after the administration
CMP	:	Clinical Monitoring Plan
CISO	:	Chief Information Security Officer
COG	:	Children's Oncology Group
CoV	:	Coefficient of Variation
CRA	:	Clinical Research Associate
CRF	:	Case Report Form
CRO	:	Contract Research Organisation
CSR	:	Clinical Study Report
CT	:	Computerized Tomography
CTCAE	:	Common Terminology Criteria for Adverse Events
CV	:	Curriculum Vitae
DAP	:	Data Analysis Plan
DPO	:	Data Protection Officer
ECG	:	ElectroCardioGram
ECOG	:	Easter Cooperative Oncology Group
eCRF	:	Electronic Case Report Form
EEA	:	European Economic Area
e.g.	:	Exempli gratia (for example)
ELISA	:	Enzyme-Linked Immunosorbent Assays
EMA	:	European Medicines Agency
ERIN	:	Event Requiring Immediate Notification

EU	:	European Union
FAS	:	Full Analysis Set
FDP	:	Fibrin Degradation Product
g	:	gram
G/L	:	Giga (10^9) per litre
GCP	:	Good Clinical Practice
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
GMR	:	Geometric Mean Ratio
h	:	hour
HBs	:	Surface antigen of Hepatitis B virus
HCV	:	Hepatitis C virus
HDL	:	High-Density Lipoprotein
HEV	:	Hepatitis E virus
HIV	:	Human Immunodeficiency Virus
HR	:	Heart Rate
I.R.I.S.	:	Institut de Recherches Internationales Servier
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonisation
ICTR	:	International Centre for Therapeutic Research
i.e.	:	id est (that is)
IEC	:	Independent Ethics Committee
IM	:	Intra Muscular
IMP	:	Investigational Medicinal Product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial (test drug / placebo / reference product)
INR	:	International Normalized Ratio
IRS	:	Interactive Response System
IV	:	IntraVenous (route)
kg	:	kilogram
L	:	Litre
LDH	:	Lactate DeHydrogenase
LDL	:	Low-Density Lipoprotein
LFT	:	Liver Function Test
LVEF	:	Left Ventricular Ejection Fraction
MAH	:	Marketing Authorization Holder
MedDRA	:	Medical Dictionary for Regulatory Activities
MRI	:	Magnetic Resonance Imaging
MUGA scan	:	Multi-Gated Acquisition scan
NASH	:	Non-Alcoholic SteatoHepatitis
NCCN	:	National Comprehensive Cancer Network
NCA	:	Non-Compartmental Analysis
NCI	:	National Cancer Institute
NGO	:	Non-Governmental Organization
NIMP	:	Non-Investigational Medicinal Product (backbone regimen used in the frame of ALL-MB 2015 protocol)
µmol	:	micromole
mg	:	milligram

min	:	minute
mL	:	millilitre
NA	:	Not Applicable
PAA	:	Plasma Asparaginase Activity
PBS	:	Phosphate-Buffered Saline
PCR	:	Polymerase Chain Reaction
PEG	:	PolyEthylene Glycol
PD	:	PharmacoDynamics
PK	:	PharmacoKinetics
PKAS	:	Pharmacokinetic Analysis Set
PS	:	Performance Status
PT	:	Prothrombin Time
RBC	:	Red Blood Cells
RMP	:	Risk Management Plan
RNA	:	Ribonucleic Acid
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SAS	:	Safety Analysis Set
SD	:	Standard Deviation
sec	:	second
SmPC	:	Summary of Product Characteristics
SWFI	:	Sterile Water for Injection
t½z	:	terminal half-life
TEAE	:	Treatment Emergent Adverse Event
test drug	:	Drug substance in a given dosage form, tested in a clinical trial. In this study, it corresponds to the lyophilized S95014
Tmax	:	time corresponding to Cmax
TSH	:	Thyroid Stimulating Hormon
U	:	Unit
ULN	:	Upper Limit of reference range
US	:	United States
V	:	Visit
WBC	:	White Blood Cells
WHO-Drug	:	World Health Organization Drug Dictionary
WOCBP	:	Woman of Child Bearing Potential

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non sponsor parties, sponsor parties and CRO responsible for local management of the study are described in a separate document entitled Administrative part of clinical study protocol.

The list of investigators is described in a separate document attached to the protocol and entitled "List of investigators".

2. BACKGROUND INFORMATION

2.1. Overview of disease epidemiology and current treatment

Leukemia is the most common pediatric malignancy. Acute lymphoblastic leukemia (ALL) is typically characterized by the proliferation of large number of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is the most common type (46.6%) of acute leukemia in childhood and the most commonly diagnosed cancer in children (25%) (Esparza, 2005; Noone et al, 2018). Approximately 1000 children are newly diagnosed with ALL each year in Russia (Kaprin, 2019).

The treatment of ALL includes long-term use of multiagent chemotherapy (National Comprehensive Cancer Network clinical practice guidelines), of which asparaginase is a cornerstone component (Hoelzer D et al, 2016, Asselin B et al, 1999). Asparagine is a nonessential amino acid for normal cell growth but is considered essential for leukaemic cells as these cells are dependent on exogenous sources of asparagine for survival. Asparaginase selectively kills leukaemic cells by depleting asparagine levels. (Asselin B et al, 1999). Native *Escherichia coli*-derived L-asparaginase (*E. coli* L-asparaginase) is one of the asparaginase preparations that have been used for the treatment of ALL since 1970s; however, its use is associated with high immunogenicity, which can be manifested by the occurrence of hypersensitivity reactions (Silverman LB et al, 2010) and/or the neutralization of asparaginase activity without any signs of hypersensitivity (i.e. silent inactivation) (Tong WH et al, 2014). Moreover, E. coli L-asparaginase must be administered frequently (i.e. three times weekly), as the drug has a very short elimination half-life (Asselin B et al, 1999).

Consequent to these limitations, pegylated formulations of *E. coli* L-asparaginase have been developed, including pegaspargase (Oncaspar®) [with a succinimidyl succinate linker].

The worldwide standard treatments for pediatric ALL include the treatment protocols established by the Children's Oncology Group (COG) and the Berlin-Frankfurt-Munster (BFM) group. In Russia, approximately 90% of newly-diagnosed pediatric patients with ALL are treated in compliance with the ALL-MB 2015 protocol (see Appendix 1).

2.2. S95014

Detailed information on the nonclinical and clinical experience with S95014 is provided in the latest version of the Investigator's Brochure.

2.2.1. Mechanism of action of S95014

The mechanism of action of L asparaginase is the enzymatic cleavage of the amino acid asparagine into aspartic acid and ammonia, with subsequent depletion of asparagine in the blood plasma. Since

lymphoblastic tumor cells, unlike healthy cells, appear to be unable to synthetize asparagine, the asparagine depletion results in inhibition of cell protein synthesis and therefore in their destruction. Hence, when plasma levels of L-asparagine decrease, intracellular levels of L-asparagine become markedly low, protein synthesis is inhibited, and leukemic cells undergo apoptosis. Unless an extracellular supply of L-asparagine is available, L-asparaginase is a specific chemotherapeutic agent for leukemic cells while preserving non-leukemia cells. The goal of asparaginase therapy is sustained systemic depletion of asparagine.

2.2.2. S95014 pharmacokinetics

Pharmacokinetic assessments of S95014 were based on an enzymatic assay measuring asparaginase activity after IM (CCG-1962 study) and IV (AALL07P4, DFCI 11-001 studies) administration.
In study AALL07P4, following a single 2500 U/m² IV dose of S95014 during the induction phase, a C_{max} of 1.6 U/mL is reached in 1.25 hour; the area under the asparaginase activity time curve (AUC) from time zero to infinity (AUC_{inf}) is 16.6 U/mL/day. Also, 95.3% of ALL patients sustained asparaginase activity ≥ 0.1 U/mL for 18 days (Angiolillo, 2014).
After single and repeated 2500 U/m^2 doses of S95014, clinically relevant asparaginase activity is maintained over the entire dosing interval of two weeks. In study DFCI 11-001, following a single dose of IV S95014 at 2500 U/m^2 during the induction phase, 93.5% of ALL patients sustained asparaginase activity ≥ 0.1 U/mL for 18 days. Furthermore, following biweekly dosing of IV S95014 during the post-induction phase, a nadir asparaginase activity of > 0.4 U/mL is seen in all patients from weeks 7–25 (Vrooman, 2019).

For more details please refer to the last version of the Investigator's Brochure.

2.2.3. Pegylated asparaginase development and status

Oncaspar® (pegaspargase; S95014) is a variation of the enzyme L-asparaginase modified by covalently bonding units of monomethoxy polyethylene glycol (PEG) to the enzyme, forming the active pharmaceutical ingredient PEG-L-asparaginase.

In the United States (US), S95014 received approval in 1994 for second-line use in acute lymphoblastic leukaemia (ALL) following the development of hypersensitivity to native L-asparaginase. In 2006, the US authorization of S95014 was expanded to include first-line treatment of ALL.

Pegaspargase is now very well established in clinical practice in the first-line treatment of ALL and is licensed in many countries (Heo YA et al, 2019). It has been determined by the World Health Organization (WHO) an essential medication needed to meet the needs of a health system and is included in the List of Essential Medicines (WHO 2019).

The safety profile of pegaspargase has also been well characterized over these last 25 years of consistent use in ALL treatment protocols. The most common (>5%) grade ≥3 AEs included hepatotoxicity (elevated transaminases, increased bilirubin and hypoalbuminemia), febrile neutropenia, hypertriglyceridemia, hyperglycemia, pancreatitis, coagulopathy, embolic and thrombotic events, and hypersensitivity. For further details, please refer to the last version of the Investigator's Brochure.

So far, S95014 is not approved yet in Russia and the product is only available through a non-governmental organization (NGO) special request. Thus, patients treated in ALL-MB 2015 protocol

are administered S95014 during the induction phase (one dose) and native L-asparaginase during the consolidation phase. Once approved, S95014 is expected to play an important role in Russia as a first-line treatment for ALL.

2.2.4. Development of a lyophilized S95014 formulation

Different formulations containing different quantitative and qualitative compositions of cryoprotectants were investigated to identify the best product composition that could withstand the lyophilization process and guarantee the production of high-quality drug product with improved stability. The lyophilized S95014 powder for Injection is provided in a single-use vial which after reconstituted will contain 3,750 U/5mL of active PEGylated L-asparaginase [750 U/mL after reconstitution with 5.2 mL of sterile water for injection (SWFI)], which is equivalent to the strength of liquid S95014. The lyophilized S95014 formulation has a longer shelf-life as compared to the liquid formulation (36 months vs 8 months).

A comparative, single-dose and 4-week repeat dose, pharmacokinetic and pharmacodynamic preclinical study of IV administered liquid and lyophilized S95014 formulations was performed in dogs. In this study, lyophilized S95014 has been demonstrated to be equivalent to the original liquid S95014.

S95014 liquid formulation had been authorized by centralized review procedures in 28 countries in the European Union (EU) and 3 countries in the European Economic Area (EEA) in first line treatment of ALL in 2016. The lyophilized formulation of S95014 demonstrated pharmacokinetic/pharmacodynamic comparability through comprehensive analytical and non-clinical comparability assessment recommended by the Committee for Medical Products for Human Use (CHMP) of the European Medicines Agency (EMA). Consequently, the use of lyophilized formulation for S95014 was approved by centralized review procedures in 28 countries in the EU and 3 countries in the EEA in 2017.

2.2.5. Study rationale and design

This phase II, parallel, open-label single dose pharmacokinetics (PK) study aims to demonstrate the pharmacokinetic comparability of both liquid and lyophilized S95014 formulations in newly-diagnosed paediatric ALL patients.

S95014 will be intravenously administered at the labelled dose of 2500 U/m², during the induction phase, in at least 78 paediatric patients. Patients will receive other backbone chemotherapeutic regimen as per ALL-MB 2015 protocol (see Appendix 1).

Lyophilized S95014 formulation is widely used in many European countries since its approval in 2017. Moreover, the review of the safety information from post-marketing setting globally has not revealed any noticeable differences between the two presentations. For further details about the risks of lyophilized S95014 administration, please refer to the latest version of the Investigator's Brochure.

The study will be conducted in compliance with the protocol, GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary objective

To compare the pharmacokinetics (PK) of both lyophilized and liquid S95014 formulations during the induction phase after a single IV dose in newly diagnosed paediatric patients with ALL

3.2. Secondary objectives

- To describe the PK of S95014 after administration of either lyophilized or liquid 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 ≥0.1 U/mL after the administration of either lyophilized or liquid S95014
- To assess the immunogenicity of both lyophilized and liquid S95014 formulations

3.3. Exploratory objectives

Not applicable

3.4. Endpoints

Table (3.4) 1 - Endpoints

	Objectives	Endpoints
Primary	To compare the PK of both lyophilized and liquid S95014 formulations during the induction phase after a single IV dose (2500 U/m²) in newly diagnosed paediatric patients with ALL	PK parameters of S95014 in plasma (C_{max}, AUC)
Secondary	- To describe the PK of S95014 after administration of either lyophilized or liquid formulation - To evaluate the achievement of PAA of ≥0.1 U/mL after the administration of either lyophilized or liquid S95014 - To assess the immunogenicity of both lyophilized and liquid S95014 formulations - To evaluate the occurrence of TEAEs including SAEs, regardless of causality and severity, based on NCI CTCAE 5.0	Additional PK parameters from the ones defined as primary endpoints (e.g. C_{trough} 14 days post-dose, T_{max}, $T_{1/2}$) PAA on Day 10, Day 17, Day 21 and Day 28 of induction (7, 14, 18- and 25-days post dose) Anti S95014 ± anti-PEG antibodies at pre-dose, 14 days and 25 days post dose Safety tolerance profile of S95014 assessed by incidence and severity of AEs and SAEs - Laboratory tests: haematology with differential, blood biochemistry, coagulation, urinalysis, hepatitis markers and pregnancy test - vital signs and performance status

Please refer to section 7, 8, and 9 for further details.

4. STUDY DESIGN

4.1. Investigational plan

4.1.1. Study plan

This is a multicentre, national, randomized, open-label, phase II clinical study comparing the pharmacokinetics of lyophilized and liquid Pegaspargase (Oncaspar®, S95014) formulations in the treatment of newly diagnosed, untreated pediatric patients with ALL. Considering the risk of immunogenicity and hypersensitivity with S95014, it was decided to conduct a parallel study.

Written informed consent and assent (when appropriate) will be obtained from each patient and/or his/her parent(s)/legal representative before initiation of study procedures (see section 13.3). Patients will undergo screening after giving informed consent and will be included once all eligibility requirements for the study have been met. Baseline evaluations and risk stratification will be performed in compliance with the current ALL-MB 2015 protocol.

Each patient will be randomly assigned (1:1) to either lyophilized (arm 1) or liquid (arm 2) S95014 intravenously at the dose of 2500 U/m² at Day 3, in combination with other backbone chemotherapy agents as per local practice (see Appendix 1).

The study duration will be approximately 1.5 month, including the screening (14 days) and the treatment period consisting of the induction phase (approximately 30 days). After completing the induction phase, patient will be discontinued from the study and, provided that the inclusion/non-inclusion criteria are fulfilled, will be proposed to enter into a roll-over study (CL2-95014-003) for the consolidation phase.

For more details about the statistical analyses and the sample size calculation please refer to the Section 10.

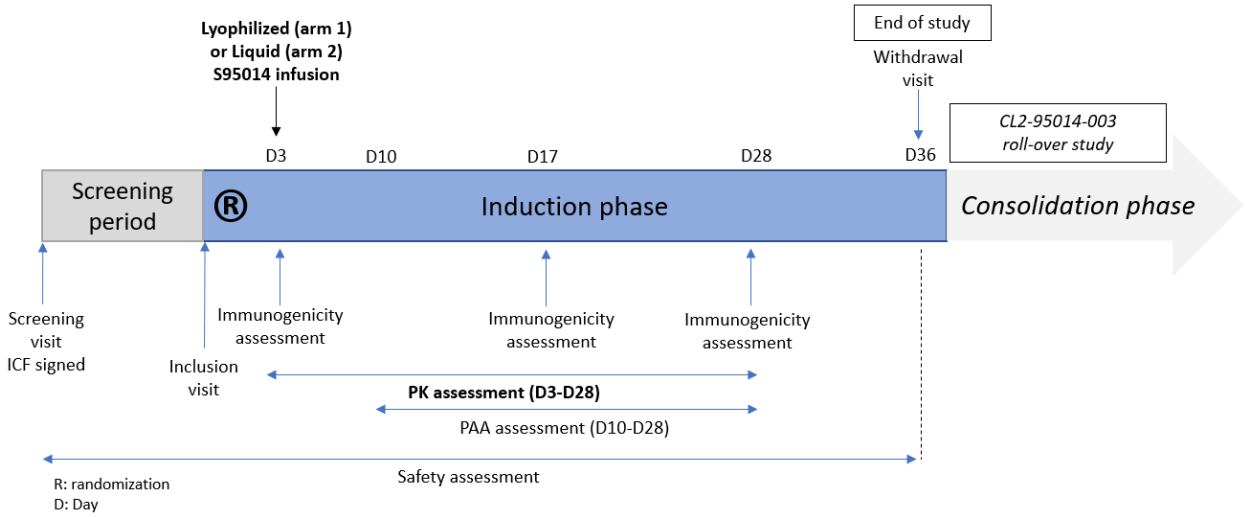
The study plan is shown in Figure (4.1.1) 1.

In case of non-inclusion of a participant, it is the investigator's responsibility to ensure, in accordance with the local standards of care and medical practices that:

- The reason of non-inclusion is explained to the participant,
- Any event associated with any procedure/condition required by the study protocol (e.g. an event occurring following the discontinuation of a forbidden treatment) is collected,
- An adequate alternative medical care is proposed to the participant.

A non-inclusion visit is not mandatorily carried out, provided these requirements are met and documented in the medical file of the participant.

Figure (4.1.1) 1 – Study plan



The study will be divided into the following periods for each participant:

- **Screening visit (up to 14 days prior to inclusion):** to obtain informed consent and check the screening/non-screening criteria.
- **Screening period (Day -14 to Day -1):** to check the eligibility of the patient to be included and randomized in the study within 14 days prior to the inclusion.
- **Inclusion visit (Day 0)**: to check inclusion/non-inclusion criteria and to confirm inclusion of the patient in the study
- **Randomization (Day 3):** the day of S95014 infusion (i.e. Day 3), included patients will be randomly assigned to one of the two treatment groups:
  - Lyophilized S95014 (arm 1)
  - Liquid S95014 (arm 2)
- **Treatment period:** treatment period will start from the day of S95014 infusion, corresponding to Day 3 of the induction phase, until the withdrawal/end-of-study visit.
- **Withdrawal/End-of-study visit:** at least 30 days after S95014 infusion (i.e. Day 33) and before starting the consolidation phase. During the withdrawal/end-of-study visit, patients will be proposed to participate in a roll-over study (CL2-95014-003) for the consolidation phase using lyophilized S95014 in combination with backbone regimen as per ALL-MB 2015 protocol.

The study start is defined as the date of the first visit of the first participant.

End of Trial is defined as the date of the last visit of the last participant.

4.1.2. Investigation schedule

Table (4.1.2) 1 describes the measurement of efficacy and safety assessed during the study

Table (4.1.2) 1 - Investigation schedule

	Screening visit	**Screening period – Inclusion**	**Induction phase**										**Withdrawal/ End-of-study visit**
			D3	*D4*	*D5*	*D8*	*D10*	*D12*	*D17*	*D21*	*D24*	*D28*	
Informed consent	X												
Screening criteria	X												
Height / Weight / BSA		X	X										
Inclusion / exclusion criteria		X											
Relevant medical / surgical history	X												
Previous treatments	X												
Concomitant treatments	X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)		X											X
IRS randomization		X											
S95014 administration			X *(see section 6.1)*										
NIMP administration			*See Appendix 1*										
Pharmacokinetic assessment													
Blood samples			X *pre-dose, just after the infusion, 4h after the end of infusion*	X *24h after the end of infusion*	X *48h after the end of infusion*	X	X	X	X	X		X	
Pharmacodynamic assessment													
Plasma Asparaginase Activity							X[2]		X[2]	X[2]		X[2]	
Immunogenicity assessment													
Blood samples			X *pre-dose*						X			X	
Safety assessments													
Vital signs		X	X *pre-dose, post-infusion*										X
Physical examination / ECOG		X	X *pre-dose, post-infusion*										X
ECG		X	X *(see section 8.2)*										X
Cardiac imaging[1]		X											X
Adverse events		X	X										X
Laboratory examinations													
Blood haematology		X	X				X		X		X		X
Blood biochemistry		X	X				X		X		X		X
Blood coagulation		X	X				X		X		X		X
Urinary biochemistry		X	X				X		X		X		X
Hepatitis serology		X											X

[1] If echocardiography is performed within 14 days before signed consent, results could be used to assess patient's inclusion in order to avoid unnecessary exam
[2] Samples collected for PAA assessment will be the same as for PK assessment to avoid duplicating sample collection

For further practical details, methods of measurement are provided in sections 7, 8 and 9.

The maximum total volume of blood collected per participant during the study will be 200 mL. Additional blood samples will be collected in the frame of the ALL-MB 2015 protocol, as per local practice.

4.2. Measures to minimise bias

This is a multicentre, randomized, open-label study. Subjects will be randomized to the liquid and lyophilized formulations according to a 1:1 ratio. The randomization will not be adaptive. No stratification factor will be used during randomization. The randomization will be centralized with an Interactive Response System (IRS).

During the study, pharmacokinetics, PAA and immunogenicity analysis will be performed in a specific central laboratory which will minimise the variability of measurements.

4.3. Study products and blinding systems

4.3.1. Products administered

S95014 liquid (reference drug) and S95014 lyophilizate (test drug) are both IMPs and will be manufactured under the responsibility of Les Laboratoires Servier Industrie (Gidy, France).

Currently, S95014 is not authorized in Russia in any of its formulations.

Table (4.3.1) 1 provides a description of the IMPs.

Table (4.3.1) 1 – Description of the IMPs (both S95014 formulations)

	S95014 Liquid	**S95014 Lyophilizate**
Pharmaceutical form **Unit dosage**	Solution for infusion 3750 U /5 ml vial	Powder for solution for infusion 3750 U /5 ml vial
Appearance, colour	Colourless solution	Lyophilized drug product: White to off white cake Reconstituted drug product: Colourless solution
Composition (Component/ Amount per mL/ Function)	Each vial contains 750 U S95014 active ingredient per mL, monobasic sodium phosphate and dibasic sodium phosphate as buffering agent, sodium chloride for tonicity and water for injections QS to 1 ml as solvent	Each vial contains 4050 U S95014 active ingredient, sucrose as lyoprotectant, sodium phosphate monobasic and dibasic as buffering agents, sodium chloride for tonicity, sodium hydroxide and hydrochloric acid for PH adjustment. After reconstitution with 5.2 ml SWFI the vial contains 750 U / ml or 3750 / 5ml S95014 active ingredient

Table (4.3.1) 2 provides a description of the packaging of the IMPs.

Table (4.3.1) 2 – Description of S95014 packaging

Number of units of the pharmaceutical form per primary packaging	- 3750 U S95014 /5 mL solution for infusion in an individual clear glass vial - 4050 U of S95014 powder for solution for infusion in an individual clear glass vial
Number of primary packaging per secondary packaging	1 vial of S95014 liquid per box 1 vial of S95014 lyophilizate per box
Number of secondary packaging per patient and per treatment period	The number of vials per patient will depend on the patient's BSA

The labelling of packages complies with the regulatory requirements of the country involved in the study.

Backbone therapy drugs will be administered as per ALL MB 2015 protocol (see Appendix 1). They will be regarded as NIMPs and will not be provided by the Sponsor. For further information about the NIMPs, please refer to section 6.1.2.

4.3.2. IMP management

S95014 liquid (reference drug) and S95014 lyophilizate (test drug) are both IMPs and will be manufactured under the responsibility of Les Laboratoires Servier Industrie (Gidy, France).

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to section 6.2), accountability and collection are the responsibility of the investigator and/or pharmacist of the medical institution.

IMP receipt and dispensing will be managed through an IRS.

Specific handling conditions and cleaning procedures will be described in the Pharmacy Manual.

Stability and storage

The IMP should be stored in a secure area with restricted access. Specific storage conditions are mentioned on IMP labelling and are detailed in the Investigator's Brochure.

The investigator/pharmacist is responsible for the IMP temperature monitoring daily using FONT-CIRT-FORM-311 "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document.

In case of temperature deviation, the investigator/pharmacist should immediately:
- block the IRS for the concerned IMPs and place them in quarantine,
- alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the instructions received.

Furthermore, the investigator/pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence.

IMP management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all the documents provided by the sponsor concerning IMP management (therapeutic unit tracking form or an equivalent document…). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfil.

The investigator and/or the pharmacist of the medical institution should only use the IMP provided for the participants involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor, and to the IRS. The investigator will notify the monitor of all complaints set out by a participant (appearance…).

In the event of anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will verify the presence of the IMP on site at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document.

Destruction

Destruction of the IMP is the responsibility of the sponsor and/or the investigator and/or the pharmacist of the medical institution.

Used remaining treatments will be locally destroyed and unused IMPs will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management.

A certificated destruction for unused IMPs will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. The practical procedures for destruction of unused IMP will be defined by the sponsor and adapted to the centre. An IMP collection and destruction form will be completed before the shipment of IMP to destruction. Destruction of IMP may be possible when the product has been used, has expired or after at least the last visit of the last treated participant.

4.3.3. Management of blinding systems

Not applicable

4.4. Discontinuation of the study or temporary halt

4.4.1. Premature discontinuation of the study or temporary halt

This study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause.

After having informed the national coordinator, the sponsor or the Independent Ethics Committee (IEC) or the Competent Authority may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the national coordinator. The IEC and Competent Authority will be informed according to local regulations.

If the study is prematurely discontinued, the on-going participants should be seen as soon as possible, and the same assessments as described in section 5.8 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, the Independent Ethics Committee (IEC) and Competent Authority.

4.4.2. Premature discontinuation of the study in an investigator site (early site closure)

The sponsor reserves the right to close a study site at any time for any sufficient reasonable cause at the sole discretion of the sponsor.
The investigator may also initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local Competent Authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

The IEC(s) and Competent Authorities will be informed according to local regulations.

4.4.3. Discontinuation of the study in the event of objective reached

Not applicable

4.5. Source data

Patient's medical file (e.g. ECG report, clinical laboratory examination's reports and all other patients' examination results), PK requisition forms will be considered as source documents.

Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study.

5. SCREENING AND WITHDRAWAL OF PARTICIPANTS

5.1. Screening criteria

5.1.1. Demographic characteristics

1. Male or female patient aged ≥ 1 to < 18 years

5.1.2. Medical and therapeutic criteria

2. Patients with cytologically confirmed and documented newly diagnosed ALL according to NCCN guidelines 2020 (see Appendix 2), excluding B-cell Burkitt ALL
3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2
4. Women of childbearing potential (WOCBP) must use a highly effective method of birth control (both described in section 5.5) during study treatment and for 6 months after the last dose of IMP. In case of use of oral contraception women should have

been stable on the same contraceptive drug (i.e. same active principle) for at least 1 month prior to the first IMP administration. In case of use of hormonal contraception, WOCBP and male participants with WOCBP partners should use a second method of contraception, also called barrier method, such as male or female condoms, cap, diaphragm or sponge with spermicide. However, since there is a potential for an indirect interaction between S95014 and oral contraceptives, the concomitant use of S95014 and oral contraceptives is not recommended. A method other than oral contraceptives should be used in WOCBP.

5. Male participants with WOCBP partners must use a condom during the study and until at least 6 months after the last dose of IMP. In addition, contraception should be considered for their female partners. Contraceptive measures do not apply if the participant is sterile, vasectomized or sexually abstinent. Sperm donation will not be allowed during the study and for 6 months after the last dose of IMP.

5.1.3. Informed consent

Obtained as described in section 13.3 of the protocol.

5.2. Non-screening criteria

5.2.1. General criteria

6. Unlikely to cooperate in the study
7. Pregnant and lactating women
8. Participation in another interventional study at the same time; participation in non-interventional registries or epidemiological studies is allowed
9. Participant already enrolled in the study (informed consent signed)

5.2.2. Medical and therapeutic criteria

10. Prior treatment with chemotherapy or radiotherapy (except steroids and intrathecal therapy)
11. Prior surgery or bone marrow transplant related to the studied disease
12. Down Syndrome
13. Psychiatric illness/social situation that would limit compliance with study requirements
14. Known carriers of HIV antibodies
15. History of previous or concurrent malignancy
16. History of sensitivity to polyethylene glycol (PEG) or PEG-based drugs
17. Pre-existing known coagulopathy (e.g. haemophilia and known protein S deficiency)
18. Known history of pancreatitis
19. Known history of significant liver disease
20. Significant laboratory abnormality likely to jeopardize the patients' safety or to interfere with the conduct of the study, in the investigator's opinion
21. Severe or uncontrolled active acute or chronic infection
22. Uncontrolled intercurrent illness including life-threatening acute tumor lysis syndrome (e.g. with renal failure), symptomatic congestive heart failure, cardiac arrhythmia

5.3. Inclusion criteria

Screening criteria must still be fulfilled at the time of the inclusion visit

5.4. Non-inclusion criteria

Non-screening criteria must still be fulfilled at the time of the inclusion visit

5.4.1. General criteria

23. Women of childbearing potential tested positive in a serum pregnancy test within 7 days prior to the treatment period

5.4.2. Medical and therapeutic criteria

24. Inadequate hepatic function (total bilirubin > 1.5 times upper limit of normal (ULN), transaminases > 5 x ULN)
25. Inadequate renal function defined as serum creatinine > 1.5 x ULN

5.5. Definition of women of childbearing potential and contraception methods

Women of childbearing Potential
A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception methods
Definition of highly effective contraception methods for the study:

Highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, male sterilization (vasectomy).

5.6. Retest management during screening period

A patient who has a laboratory result(s) that does not satisfy the entrance criteria may have the test (s) repeated once providing that the investigator judges it relevant according to the patient / participant previous results, or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the patient/participant will not be required to sign another informed consent, and the original patient / participant ID number assigned by the investigator will be used.
In any case, the last result available for each parameter must be considered for the patient/participant inclusion.

5.7. Additional information recorded at the inclusion visit

Not applicable

5.8. Participant withdrawal

5.8.1. Withdrawal criteria

Information to be collected during the last visit of these participants is given in section 5.8.2. These follow-up modalities are used to ensure safety evaluation of all participants who received the IMP.
The reasons for premature discontinuation of the study are:

- **Adverse events** according to the judgement of the investigator, including no recovery of safety parameters, serious hypersensitivity or adverse events delaying the IMP administration by more than 14 days (see section 6.1.1)
- **Pregnancy**
- **Major deviation to protocol** if it interferes with the study evaluations and/or if it jeopardises participant's safety
- **Non-medical reason** (e.g. consent withdrawal, participant's removal)
- **Other, physician decision**

5.8.2. Procedure

Upon discontinuation of treatment the investigator must:

- Notify the Clinical Research Associate (CRA) immediately
- Indicate the main reason, if there are several reasons
- Record this information in the eCRF

In the case of premature withdrawal from the study due to an adverse event (event requiring immediate notification or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see section 8.9). This information is recorded in that part of the electronic case report form which concerns adverse events. If the investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the participant.
If the study is stopped as a result of an event requiring immediate notification, the procedure described in section 8.9.2.5 is to be implemented.

After discontinuation of the study, the participants' treatment is left to the physician's discretion, according to local regulation and practice. Provided that the inclusion/non-inclusion criteria are fulfilled, the participant will be proposed to enter a roll-over study (CL2-95014-003) using lyophilized S95014 during the consolidation phase, in compliance with ALL-MB 2015 protocol.

5.8.3. Lost to follow-up

Not applicable

6. TREATMENT OF PARTICIPANTS

6.1. IMPs and NIMPs administered

6.1.1. IMPs

S95014 liquid (reference drug) and S95014 lyophilizate (test drug) are both IMPs.

Either lyophilized S95014 (arm 1) or liquid S95014 (arm 2) will be administered IV at the dose of 2500 U/m² at Day 3 of the induction phase, over 1-hour infusion. Please refer to latest version of the Investigator Brochure for further details.

S95014 dosage is calculated according to body surface area (BSA). The BSA will be calculated by the IRS based on the height and weight measured on the day of S95014 infusion (all BSA calculations are rounded to 2 decimal places). Height and weight measured within 4 days before the date of S95014 infusion will be acceptable.
BSA (m²) = √ (Height [cm] x Weight [kg]/3600)

Study sites are required to use only calibrated and certified scales throughout the study.

If, for any reason, a patient included in the study is not able to receive S95014 at the prescribed dose of 2500 U/m² at the planned day, the infusion can be delayed. The day of S95014 administration will be regarded as Day 3 and the other treatments (backbone regimen used in the frame of ALL-MB 2015) will be postponed consequently. No dose reduction will be authorized during the induction phase. Beyond 14 days, if the patient cannot receive the IMP, he/she must be discontinued from the study.

6.1.2. NIMPs

Backbone therapy drugs administered as per ALL MB 2015 protocol (see Appendix 1) will be regarded as NIMPs and will not be provided by the Sponsor.

NIMPs used during the induction phase are, as follows:
- Dexamethasone
- Methylprednisolone
- Vincristine
- Daunorubicin
- Idarubicin
- Methotrexate/cytarabine/prednisolone intrathecal

For further details about NIMPs, please refer to respective SmPC.

6.2. IMP dispensing

The treatment group will be allocated via IRS using a central randomization (1:1) to either lyophilized S95014 (arm 1) or liquid S95014 (arm 2) of the induction phase (see Pharmacy manual for further details).

IMPs will be dispensed by the pharmacist/responsible of the healthcare establishment upon prescription of the investigator only.

The investigator may only use the IMPs provided for the patients involved in the study and treated under his/her responsibility or that of a designated co-investigator.

For each patient, the IMPs will only be dispensed during the study.

Further instructions for the preparation and dispensation of S95014 are described in the Pharmacy Manual.

The detachable portion of the label on the IMP box must be stuck by the investigator on an IMP label collection form or on the prescription form where the IMPs are dispensed by a pharmacist.

6.3. Previous and concomitant treatments

If a patient receives any drug other than S95014 and backbone therapies used in the frame of ALL-MB 2015 during the period from the day of informed consent to the withdrawal/end-of-study visit, the following information will be entered in eCRF:

- Name of drug or therapy
- Start date and end date of treatment
- Route of administration
- Indication

The following treatments are to be used with caution during the treatment period:

- Live vaccines
- Coumarin/warfarin and heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory medicines (e.g. ibuprofen, naproxen).
- Prednisone, methotrexate, vincristine, cytarabine (see ALL-MB 2015 protocol for further details)

For further information about the drug-drug interactions, please refer to the latest version of the Investigator Brochure.

The patient and his/her parent(s)/legal representative must be told to notify the investigational site about any new medications he/she takes after having signed the ICF of the study. All medications (other than study drugs) and significant non-drug therapies (including blood transfusion) administered during the study must be listed on the eCRF.

6.4. IMP compliance

The number of injectable vials dispensed are to be counted by the investigator or a designated person from his/her team and recorded in the electronic case report form and therapeutic unit tracking form, or an equivalent document.

The compliance will be assessed from the method described above.

6.5. Discontinuation of the IMP

Not applicable

7. ASSESSMENT OF PHARMACOKINETICS

7.1. Methods and measurement times

Pharmacokinetics measurements performed during the study are indicated in Table (4.1.2) 1.
The sampling conditions, labelling, handling and storing details will be described in a specific technical document.

Sampling methods & timepoints:

Eleven (11) sodium heparinised plasma for pharmacokinetic (serial PK samples) will be obtained; as follows: pre-dose, just after the end of infusion (on Day 3), 4 hours after the end of infusion (on Day 3), 24 hours after the end of infusion (on Day 4), 48 hours after the end of infusion (on Day 5), 120 hours (i.e. 5 days) after the end of infusion (on Day 8), 168 hours (i.e. 7 days) after the end of infusion (on Day 10), 216 hours (i.e. 9 days) after the end of infusion (on Day 12), 336 hours (i.e. 14 days) after the end of infusion (on Day 17), 432 hours (i.e. 18 days) after the end of infusion (on Day 21) and 600 hours (i.e. 25 days) after the end of infusion (on Day 28).

In all participants, 2.5 mL of blood will be taken at each timepoint for pharmacokinetic assessment, leading to a total volume of 27.5 mL (11 timepoints overall).

All samples should be obtained as closely as possible to the nominated time and at least within the following windows:

- Pre-dose: within 15 minutes before IMP administration (start of infusion),
- End of infusion and 4-hour time point: + 10 min after the end of the infusion and ± 10 min for 4-hour timepoint
- 24-hour and 48-hour post-dose samples: ± 1 hour of the nominated time
- 5- 7- and 9-days post-dose (i.e. Day 8, Day 10 and Day 12) samples: ± 3 hours of the nominated time
- 14-, 18- and 25-days post-dose (i.e. Day 17, Day 21 and Day 28) samples: ±6 hours of the nominated time

The accurate sampling times must be recorded in the e-CRF.

Blood samples for end of infusion and 4-hour timepoints should be collected from the arm opposite from the IMP infusion, or from another site.

All samples will be destroyed after mandatory assessment is completed and at the latest before the final version of the clinical report.

Participant who meet any of the following criteria will not be evaluable for PK analysis and therefore will be replaced:

- infusion interrupted for any reason
- deviation in the theoretical administered dose > 10%
- at least one missing PK sample during the 48 first hours
- at least two missing PK samples after the 48-hour time point,

PAA will be determined using a coupled enzymatic activity assay, validated according to current regulatory guidelines.

The following parameters (including but not limited) will be calculated using a non-compartmental analysis (NCA) approach based on observed plasma asparaginase activity (PAA) time profiles: Area Under the Concentration-Time curve (AUC); maximum observed plasma asparaginase activity (C_{max}); lowest observed plasma asparaginase activity ($C_{trough,\ day\ 14}$) 14 days post-dose, time to reach the maximum PAA (T_{max}), terminal half-life ($T_{1/2}$). The above PK parameters will be calculated for each patient and the corresponding descriptive

statistics of PK parameters will be tabulated. (Arithmetic mean, SD, geometric mean, geometric CoV, median, min, max).

For further details about the PK analysis, please refer to the corresponding Data Analysis Plan (DAP).

8. ASSESSMENT OF SAFETY

All adverse events and other situations relevant to the safety of the participants must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table (4.1.2) 1.

Safety assessment of lyophilized vs liquid S95014 will include:
- adverse events (AEs) assessments
- physical examinations, performance status ECOG (see Appendix 3)
- laboratory assessments: haematology, blood biochemistry, coagulation parameters, urinalysis, hepatitis serology
- ECG measurements (triplicate)
- vital signs measurements

Adverse events will be collected regardless of grade or IMP relationship and will be graded according to current NCI CTCAE criteria 5.0

Any significant abnormality detected during safety assessments from the patient ICF signature until the withdrawal/end-of-study visit must be reported on the adequate eCRF page by the investigator at each visit (AE, medical history or sign & symptoms).

8.2. Methods and measurement times

Relevant medical history will be reported to identify any medical condition which could preclude patient's inclusion:
- Initial diagnosis
- Previous chemotherapies, bone marrow transplants, surgeries, radiotherapies related to the studied disease
- Concomitant signs and symptoms related to the studied disease
- Concomitant and previous treatments

Clinical examination and vital signs measurements
- Serum pregnancy test will only be performed for WOCBP (see Section 5.5)
- Complete clinical examination, height and weight measurement and ECOG PS assessment will be performed
- Vital signs measurements include blood pressure (BP), heart rate (HR) and temperature. BP and HR will be measured by an automatic device in supine position after 5 min rest.

Vital signs and performance status measurements will be performed during screening, before and after S95014 infusion (Day 3, pre-dose and post-dose) and during the withdrawal/end-of-study visit.

Laboratory tests

All laboratory tests performed during the study period will be assayed in an identified laboratory at hospital. Inter-visits laboratory tests could be assayed by local laboratories. In all cases, the full validated set of normal ranges values will be collected, as well as any update in these values during the study and must be documented in the corresponding eCRF pages.

All samples will be destroyed after mandatory assessment is completed and at the latest before the final version of the clinical report.

The laboratory parameters collection plan is described in Table (8.2) 1.
Blood haematology, blood biochemistry, blood coagulation and urinary analysis will be performed during screening, before S95014 infusion (Day 3, pre-dose), at Day 10, Day 17, Day 24 and during the withdrawal/end-of-study visit.
Other laboratory tests (i.e. hepatitis serology and pregnancy test) will be performed during screening and during the withdrawal/end-of-study visit.

Table (8.2) 1 - Local Clinical laboratory parameters collection plan

Test Category	Test Name
Haematology	Haematocrit, Haemoglobin, Red blood cells (RBC), White blood cells (WBC), Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts in absolute value and in %)
Biochemistry	Albumin, Alkaline Phosphatase (ALP), ALT, AST, Ammonia, Bicarbonates, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Phosphorus, Sodium, Potassium, Creatinine, Total Bilirubin, Total Cholesterol, LDL, HDL, Triglycerides, BUN or Urea, Uric Acid Amylase, Lipase, Glucose
Urinary analysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, Protein) If the dipstick test is at least 2+ on one or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s)
Blood coagulation	Prothrombin time - International Normalized Ratio (INR), fibrinogen, protein S activity, antithrombin activity, activated Partial Thromboplastin Time (aPTT), D-dimer, FDP
Hepatitis serology	HbsAg, HbsAb, HbcAb, if HbsAg or HbcAb positive check viral load (HBV-DNA) at baseline, HCV RNA-PCR, HEV RNA-PCR
Pregnancy Test	Pregnancy testing is mandatory at inclusion (serum) and at withdrawal/end-of-study visit (serum) for WOCBP

All samplings for biochemistry should be taken in fasting conditions.

Abnormal laboratory values or test/exams results (i.e. ECG recording) will constitute an AE if they are:

- associated with signs and symptoms, or
- deemed clinically significant in the investigator's opinion, or
- if they require curative therapies, or
- associated with delay of study medication, or
- associated with study discontinuation

Triplicate Electrocardiograms (ECG) will be assessed during screening and the withdrawal/end-of-study visit. In addition, ECG results will be collected, if made available, as per ALL-MB 2015 protocol timepoints (e.g. before and after anthracyclines administration)

LVEF assessment will be performed through echocardiography or MUGA scan during screening and during the withdrawal/end-of-study visit

8.3. Definition of Adverse events

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (e.g. screening period) are also concerned).

An adverse event can therefore be:

- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary or safety evaluation scale).

Of note:

- Any **hospitalisation for administration of anti-tumoral treatment and/or associated protocol (during or after the study) or other care measures for cancer (e.g. overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (e.g. learning of diabetes management by the participant) or routine check-up should not be considered as an adverse event and should not be reported in the e-CRF. The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the e-CRF and kept in the source data (or patient file)**:
  - therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (e.g. sterilisation, wisdom teeth removal),
  - comfort procedures (e.g. cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious adverse events

Any adverse event that at, any dose:
- results in death,
- is life-threatening(1),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- is medically significant(2),
- results in persistent or significant disability/incapacity(3),
- is a congenital anomaly/birth defect(4).

(1) Life-threatening in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(2) Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of Overdose

This refers to any intake of a quantity of IMP or a product other than the IMP taken as part of the protocol (NIMP) which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol or in ALL-MB 2015 protocol for NIMP.

8.6. Definition of Adverse event of special interest

An adverse event of special interest (AEOSI) is one of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation such as hospital records and/or adjudication committee could be appropriate. It may be a serious or non-serious AE that may require further investigation in order to be characterized and understood.

AEOSI include:
- Grade ≥ 3 ALT/AST increase or grade ≥ 3 hyperbilirubinemia
- Grade ≥ 3 haemorrhage or grade ≥ 3 thromboembolic events
- Grade ≥ 3 pancreatitis
- Grade ≥ 3 hypersensitivity

Those adverse events have been identified in the Risk Management Plan (RMP) as important identified risks with S95014. A close monitoring and a specific documentation will be required, as described in sections below.

8.6.1. Hepatotoxicity monitoring

Considering the safety profile of the compound, an increase in serum liver enzymes should be followed by repeat testing including all the usual serum measures (at least ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing as follows:

- For isolated total bilirubin increase Grade 3 (> 3.0 x ULN) or isolated AST or ALT increase Grade 3 (> 5.0 x ULN), the patient should be monitored weekly including Liver Function Tests [LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 x ULN) and gamma-glutamyl transpeptidase], or more frequently if clinically indicated, until values have resolved to baseline or stabilized over 4 weeks
- For AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN, repeat liver function tests as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks

Clinically significant abnormalities have to be carefully documented in the patient's medical file.

Additional tests to evaluate liver function such as INR (or biopsy if appropriate) may be performed as appropriate. Close observation and documentation also include:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases, obtaining a history of concomitant drug use (including non-prescription and herbal and dietary supplement preparations), alcohol use
- Performing liver imaging (ultrasound, magnetic resonance or computerized tomography) to evaluate biliary tract or liver disease
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; NASH; and biliary tract disease
- Considering gastroenterology or hepatologist consultations

A specific form (see Appendix 4) will be completed.

8.6.2. Pancreatitis monitoring

Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation. A Computerized Tomography (CT) scan or other imaging test to assess the pancreas, liver, and gallbladder could be performed within 1 week of the first occurrence of any ≥ Grade 3 amylase and/or lipase increase, or as clinically indicated.

As impaired glucose tolerance may occur with concomitant use of S95014 with prednisone, blood glucose levels should be monitored.

8.6.3. Coagulopathy monitoring

Increased prothrombin time (PT), increased activated partial thromboplastin time (aPTT), and hypofibrinogenaemia 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 procoagulant or anticoagulant effects are used simultaneously, such as acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products, or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered.
In case of haemorrhage grade ≤ 2, evaluate for coagulopathy and consider clotting factor replacement as needed.

8.6.4. Hypersensitivity monitoring

Prophylactic treatment with acetaminophen, histamine-1 blocker, and corticosteroid will be administered to prevent hypersensitivity.

Patients' vital signs (BP, HR, temperature) should be monitored during S95014 infusion and for 1 hour after the end of S95014 infusion. Resuscitation equipment and other appropriate means for the treatment of anaphylaxis should be available (epinephrine, oxygen, intravenous steroids, etc.).

S95014 infusion should be interrupted in patients with serious hypersensitivity reactions and patients should be discontinued from the study (see section 5.8.1).

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (i.e. without delay and within 24 hours at the latest) to the sponsor if it is:

- a serious adverse event,
- an adverse event of special interest, (if applicable, as defined in § 8.6, otherwise delete)
- an overdose of the IMP/NIMP even if asymptomatic,
- any intake of the IMP/NIMP by a person around the participant,
- a pregnancy.

8.8. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **severity** of the event as well as the **cause-effect relationship** between an adverse event and the research (IMP or study protocol). This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation of the **expectedness** of the event (See Section 8.9.3).

The Seriousness should be evaluated according to international guidances (see definition Section 8.4, in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

The severity of all AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) on a five-point scale (Grade 1 to 5):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[1].
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The cause-effect relationship

The investigator has to assess in the AE form if the AE is related or not to the research, meaning:

- adverse event related to IMP(s)
- adverse event related to study protocol i.e. related to:
  - a procedure scheduled in the study protocol (i.e. exercise test, MRI, etc.), or
  - a change or withdrawal of previous / concomitant treatment related to the conditions of the protocol or
  - a product other than the IMP, taken as part of the protocol (NIMP or other);

Moreover, the investigator has to assess if the AE is related to disease progression. Cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the mechanism of action of the IMP…), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and IMP is at least reasonably possible (i.e. the relationship cannot be ruled out) it is to be considered as "related".

8.9. Reporting procedures

8.9.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see sections 8.3 to 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- before the first intake of the IMP for events related to the research
- at any time after the administration of IMP, up to the participant's last study visit for all events,
- up to 30 calendar days after the IMP administration for all ERIN, regardless of the supposed role of the research,
- irrespective of the time of onset in case of serious adverse event related to the research.

Of note, events occurring between the signature of the informed consent and the first administration of the IMP for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as **medical history** or as signs and symptoms related to the studied disease in the dedicated form of the CRF.

[1] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden".

8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event,
- **Assess** the event in terms of seriousness, intensity and causality,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately),
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis (where possible, the results from pre-IMP assessments should be appended for comparison with the results obtained under IMP), or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on an “Adverse event” page previously created for the event.

If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the outcome of the event will be noted on an « Adverse Event » page previously created for the event

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.9.2.3. Special situations (pregnancy, overdoses, intake of IMP/NIMP a person around the participant)

Pregnancy

If a female participant in the study becomes pregnant, the investigator must:
- stop immediately the IMP (if the pregnancy is a non-screening/exclusion criterion),
- report it on an « Adverse Event » page as well as on the specific paper pregnancy form (1st page) to be notified immediately (ERIN),
- contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).
- If the partner of a participant becomes pregnant during the course of the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP or NIMP

- In case of overdose, the investigator should report it on an "Adverse Event" page to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - dose details (number of units, duration…) and, if multiple overdose, details regarding other medicinal products or substance,
  - context of occurrence, i.e. intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
  - related signs and symptoms ("No related adverse events" to be reported otherwise),
  - outcome.
- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP/NIMP by a person around the participant

This event should not be reported in the e-CRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording Methods in the e-CRF

Adverse events must be documented on the « Adverse Event » page of the e-CRF.

In case of chronic disease:
- if the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the «Adverse Event» page previously created for the event which will clearly describe the diagnosis.

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:

- **Immediately** after being informed of this event, **fill in** the **participant's medical file** as well as the **« Adverse Event » page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into Inform, an e-mail will be immediately and automatically sent to the sponsor.
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IEC, in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes serious (ERIN), this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately send them by fax or by e-mail to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line (international prefix followed by 33.1.55.72.60.00 for a call from outside France, and/or the 24-hour phone line of the ICTR in Russia 8 495 9370700, ext. 2),
- As soon as the e-CRF becomes available, the investigator should enter these data in the « Adverse Event » page of the e-CRF.

8.9.3. Responsibilities of the sponsor

In accordance with international guidances, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the investigator, and according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product to the appropriate Authorities and to all the investigators involved. Any new safety finding likely to affect the benefit /risk balance of the product will be also notified to the trial subjects involved - through the investigators - as mentioned in 13.4 "Modification of the information and consent form"

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO PHARMACOKINETICS OR SAFETY

9.1. Assessments related to screening/inclusion criteria

See section 4.1.2.

9.2. Assessment of plasma asparaginase activity

As a secondary endpoint, the achievement of plasma asparaginase activity (PAA) ≥ 0.1 U/mL will be assessed 7, 14, 18 and 25 days after the S95014 infusion (i.e. Day 10, Day 17, Day 21 and Day 28). Samples collected for PAA assessment will be the same as for PK analysis to avoid duplicating sample collection.

PAA will be determined using a coupled enzymatic activity assay, validated according to current regulatory guidelines.

All samples will be destroyed after mandatory assessment is completed and at the latest before the final version of the clinical report.

The sampling conditions, labelling, handling and storing details will be described in a specific technical document.

9.3. Assessment of immunogenicity

The occurrence of neutralizing antibodies and associated asparaginase inactivity can be related to a potential silent inactivation, which is characterized by the formation of neutralizing antibodies and reduced asparaginase activity in the absence of a clinically evident allergic reaction (Van der Sluis, 2016).
Immunogenicity assessment will include the detection of binding antibodies against S95014 as well as antibodies against PEG in samples taken during the treatment period, at pre-dose, 14 days and 25 days post dose (i.e. Day 17 and Day 28). The test item is the presence or absence of the production of anti-drug antibodies (ADA).

This evaluation will be based on qualitative enzyme-linked immunosorbent assays (ELISA) using S95014 as coating antigen. All positive samples will be further confirmed by competitive ELISA for the presence of binding anti S95014 antibodies. Samples, when confirmed positive, will then be assayed for anti-PEG antibodies. For all these assays, antibody status (positive or negative) will be reported.

The antibody positive samples will be further diluted and tested, and the highest sample dilution with a positive result will be reported as the anti-drug antibody titer.

In the absence of a validated neutralizing antibody assay, the neutralizing potential of anti-drug antibodies in positive samples will be evaluated based on the concomitant results of the serum asparaginase activity.

All assays are validated with respect to cut-point, precision, linearity, short-term stability, freeze-thaw stability and drug interference.

Patients positive for ADA should be monitored every 3 months in the roll-over study protocol.

All samples will be destroyed after mandatory assessment is completed and at the latest before the final version of the clinical report.

The sampling conditions, labelling, handling and storing details will be described in a specific technical document.

9.4. Assessment of biomarkers

Not applicable

10. STATISTICS

The analysis methods for PK, PAA, immunogenicity and safety endpoints are specified below. Unless otherwise specified, categorical data will be summarized using frequencies and percentages, and continuous data will be summarized using descriptive statistics. The descriptive statistics will be the number of subjects, mean, standard deviation, minimum, median, and maximum.

10.1. Population

10.1.1. Determination of sample size

This study is a two-arm parallel 1:1 randomized trial to evaluate the PK comparability between liquid and lyophilized S95014 formulations. For both AUC and C_{max}, the coefficient of variation (CoV) of 0.30 is assumed based on the estimation of CoV for liquid S95014 from a previous study (Angiolillo, 2014). It is also reasonable to assume a geometric mean ratio (GMR) of 100% for C_{max} and AUC, since no impact of an absorption phase is expected because both formulations are delivered intravenously. In addition, the CMC investigations have shown that once the lyophilised formulation is reconstituted, the characteristics of the solution are comparable to the ones of the liquid formulation. Assuming a CoV of 0.30 and a true geometric mean ratio (GMR) of 100%, a total of 78 evaluable subjects (39 subjects per arm) will provide approximately 90% power to establish the PK comparability. Assuming that 10% of the included patients will not be evaluable (e.g. missing PK timepoint etc.), 88 subjects are expected to be included to allow 78 evaluable patients.

10.1.2. Analysis subset

Full Analysis Set
The full analysis set (FAS) will consist of all subjects who have been randomized in the study. Subjects will be classified according to their assigned treatment arm.

Safety Analysis Set

The safety analysis set (SAS) is defined as the set of all subjects who have received at least one dose of S95014 in the study. Subjects will be classified according to treatment received. The safety endpoints will be analysed in the safety analysis set.

Pharmacokinetic Analysis Set
The pharmacokinetic analysis set (PKAS) will include all subjects who have received at least one dose of IMP and are evaluable for PK analysis. The PK dataset will include only the subjects who had enough samples collected to provide interpretable PK results with no deviations that might have affected the PK interpretation (e.g. infusion interrupted for any reason, deviation in the theoretical administered dose > 10%, at least one missing PK sample during the 48 first hours, ≥ 2 PK samples after the 48-hour time point). The ADA-positive patients will be a priori included in the PKAS since no impact was identified based on the population PK model. Nevertheless, if any evidence of such an impact can be identified in the study, a second PKAS will be defined that will include the patients for whom none of the ADA assessment time points is positive.

Immunogenicity Analysis Set
The immunogenicity analysis set will include all subjects who have received at least one dose of IMP and have at least one post-dose sample evaluable for immunogenicity testing.

10.2. Statistical analysis

10.2.1. Pharmacokinetics analysis

The pharmacokinetic analysis will be performed on the Pharmacokinetic Analysis Set (PKAS). The PKAS is defined as all included participants having completed the treatment period without deviation affecting pharmacokinetic interpretation (see section 10.1.2).

Final analysis will be performed after the database freezing and the electronic transfer of PAA. The dataset needed for final analysis will be prepared by extraction under the supervision of Central Business Intelligence (CBI) Department from the I.R.I.S database using SAS® PC version 9.2 software or later.

A non-compartmental pharmacokinetic analysis will be performed on the individual plasma concentrations-time profiles of PAA, using the actual administration and sampling times after administration. Calculated PK parameters will be described according to a separate Data Analysis Plan (DAP) such as: Area Under the Concentration-Time curve (AUC); maximum observed plasma asparaginase activity (C_{max}); lowest observed plasma asparaginase activity ($C_{trough,\ day\ 14}$) 14 days post-dose, time to reach the maximum PAA (T_{max}), terminal half-life ($T_{1/2}$). The above PK parameters will be calculated for each patient and the corresponding descriptive statistics of PK parameters will be tabulated. (e.g. number of patients, arithmetic mean, SD, geometric mean, geometric CoV, median, min, max).

Descriptive statistics of PAA (e.g. number of patients, arithmetic mean, geometric mean, % coefficient of variation [%CV], SD, minimum, median, and maximum) will be also calculated and tabulated per sampling time. Plasma concentrations over time will be plotted in semilogarithmic and linear formats as mean ± SD and as median (Q1, Q3).

Bioequivalence tests will be used to compare pharmacokinetic parameters of asparaginase activity in lyophilized formulation versus liquid formulation using the PKAS. Individual

values of C_{max} and AUC will be logarithmically transformed prior to statistical analysis. An additional comparison will also be performed on $C_{trough, day\ 14}$ for information purpose.

An analysis of variance (ANOVA) will be performed for the natural logarithms of PK parameters (AUC, C_{max} and $C_{trough, day\ 14}$). The ANOVA model will include fixed effect for formulation. The two one-sided tests procedure will be performed on the geometric mean ratio (GMR) between test (lyophilized pegaspargase) and reference (liquid pegaspargase) treatments. This will be done via a 90% confidence interval for the ratio obtained in the framework of the ANOVA for the logarithms. The confidence interval will be 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 will be concluded if the 90% confidence interval for AUC and C_{max} GMR is within the [80.00%; 125.00%] range.

For further details about the PK analysis, please refer to the Data Analysis Plan (DAP).

10.2.2. Safety Analysis

All subjects included in the safety analyses will be evaluated by the actual treatment arms unless otherwise specified.

10.2.2.1. Adverse Events

Treatment emergent adverse events (TEAE) will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria Adverse Events (CTCAE) v5.0. Laboratory abnormalities will be classified into Common Terminology Criteria (CTC) grade according to CTCAE v5.0 and will be reported as adverse events.

Adverse events will be summarized in hierarchical tables, presenting the number and percentage of patients having at least one AE, and having at least one AE in each primary system organ class and for each preferred term using MedDRA coding. AEs will be sorted by descending frequency, and alphabetically where frequency is tied. Such summaries will be produced for all AEs, serious adverse events (SAEs), grades 3 or 4 AEs, AEs leading to study discontinuation, and AEs leading to dose-adjustment or interruption of any of the drugs of the treatment. All of these summaries will be by system organ class, preferred term, treatment group and, in some case, maximum grade. Most of the summaries will be produced twice, once for all events regardless of study treatment relationship, and once for events suspected to be study treatment related. All deaths will be listed and summarized.
All adverse events will be listed, and any other information collected (e.g., start/end dates and duration of adverse event, severity or relatedness to study medication) will be listed as appropriate.

AEOSI will be summarized separately. All such events will be identified prior to database lock.

10.2.2.2. Other Safety Evaluations

Descriptive statistics of laboratory parameters and continuous variables of vital signs and ECG will be calculated by treatment group for each time point. Shift tables for qualitative urinalysis results at each time point after the start of administration will be created. Height, weight, body surface area (BSA) and body mass index (BMI) will be summarized over visit by treatment group.

Shift tables will be provided for laboratory parameters to compare a subject's baseline laboratory evaluation relative to the worst value during the treatment period using Common Terminology Criteria for Adverse Events (CTCAE) grades. In addition, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high (including category "high and low"). Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

10.2.3. Analysis of Plasma Asparaginase Activity

Observed individual Plasma Asparaginase Activity (PAA) level 7 days (Day 10), 14 days (Day 17), 18 days (Day 21) and 25 days (Day 28) after administration of either liquid or lyophilized S95014 will be tabulated by treatment group together with descriptive statistics (Arithmetic mean, SD, geometric mean, geometric CV, median, min, max).

The number and proportion of patients achieving a PAA of ≥ 0.1 U/mL after the administration of either liquid or lyophilized S95014 among patients with evaluable Day 10, Day 17, Day 21 and Day 28 PAA data will be summarized by treatment group along with a 2-sided 95% Clopper-Pearson confidence interval (CI).

10.2.4. Population Analysis

10.2.4.1. Subject Disposition

Subject disposition will be tabulated for all subjects by summarizing the number and percentage of subjects who are included in each analysis set, completed study treatment, discontinued from the study and by the primary reason for discontinuation.

A listing will present dates of study discontinuation and the primary reason, if applicable for each subject.

10.2.4.2. Demographic and Baseline Characteristics

Demographic and baseline measurements will be summarized for the safety analysis set using standard descriptive summaries or categorical summaries, as appropriate. In addition to the summary tables, a listing will be provided for all demographic and baseline characteristics data. In addition, listing of medical history will be provided.

10.2.4.3. Concomitant Medication

Concomitant medication for each subject will be listed.

10.2.5. Immunogenicity Analysis

The assessment of anti-drug antibodies includes binding and neutralizing antibodies to S95014 and binding anti-PEG antibodies.

The number and proportion of patients having anti S95014 ± anti-PEG antibodies 14 and 25 days (i.e. Day 17 and Day 28) after the administration of either liquid or lyophilized S95014 during the induction phase will be summarized by treatment group.

Results will be reported as follows:

- Pre-existing anti-S95014 or anti-PEG antibodies: number and proportion of samples confirmed positive at baseline.
- Seroconversion upon treatment: number and proportion of samples converted from negative at baseline to positive at Day 17 and Day 28. If a confirmed positive sample at baseline has titer increase at Day 17 or Day 28 by more than 4-fold then it will be included within the seroconverters.

On a case-by-case approach, the impact of positive anti S95014 and anti-PEG antibodies will be investigated:

- On the pharmacokinetics through the temporal association of antibodies with the loss of asparaginase activity (neutralizing antibodies)
- On the safety through the temporal relationship with treatment-emergent hypersensitivity and anaphylactic reactions.

A patient starting with pre-existing antibodies (positive baseline) will not be considered for positive post-baseline anti-drug antibodies. A patient with missing baseline will be considered as negative baseline to be conservative.

10.3. Handling of Missing, Unused, and Spurious Data

Adverse events (AEs)

- Handling of unknown causality assessment:
  - If a subject experience an AE with a missing causality assessment, the relationship of the AE will be counted as “related”.
- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as “severe” and one of them is categorized as “unknown”, the severity of this AE should be counted as “severe”.
  - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as “mild” or “moderate” and one of them is categorized as “unknown”, the severity of this AE should be counted as “unknown”. A column “UNK” should be inserted for those AEs at the end of the table (before the “Total” column if applicable).

Immunogenicity

Missing baseline anti-drug antibody results will be imputed as negative.

10.4. Planned Interim Analysis

Not applicable

10.5. Procedures for Reporting Changes to the Planned Analysis

Details of planned analyses will be specified in the Statistical Analysis Plan (SAP). Changes to the planned analysis will be documented in SAP amendments. The SAP will be finalized prior to the database lock.

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the structure mentioned in Section 1.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Management of the trial in the event of National or International Public Health Emergency such as Covid-19 pandemic is described in Appendix 5.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

Training sessions may be organised for the investigators and/or instruction manuals may be given to the investigators.

12.1.2. During the study

The investigator will allow the monitor to:

- review of the study site's processes and procedures,
- verify appropriate clinical investigator supervision of study site staff and third-party vendors,
- inspect the site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult the documents relevant to the study,
- have access to the electronic case report forms (i.e. access to an analogic phone line or his/her computer),
- check that the electronic case report forms have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the electronic case report forms,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (i.e. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:
- at the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:
- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form...).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:
- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:
- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all participants,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent/assent form" document, the "Parent(s)/Legal representative information and consent form" document, the list of investigators document, the insurance documents, the SmPC or Investigator's Brochure of administered IMPs and NIMPs will be submitted to (an) IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 6) with the GCP and with the applicable regulatory requirements.

13.3. Participant information and informed consent

In any case, the participant (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is to collect written consent/assent from each participant, when of appropriate intellectual maturity and written consent from his/her parent(s) (according to local regulations)/legal representative before his/her participation in the study.

Prior to this, each participant in the presence of his/her parent(s)/legal representative should be informed by the investigator or his/her delegate to the fullest extent possible about the study in language and terms he/she is able to understand. The investigator should also inform the parent(s)/legal representative of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of IMPs and NIMPs. The participant must be informed that he/she has the possibility not to participate in the study and that he/she is free to reconsider his/her assent at any time.

The parent(s)/legal representative of the participant and the participant* will be provided with an information and consent/assent form in clear, simple language. The participant and his/her parent(s)/legal representative must be allowed ample time to inquire about details of the study and to decide whether to participate in the study.

Two original legal representative information and consent forms must be completed, co-signed and dated personally by participant's parent(s)/legal representative and by the person responsible for collecting the informed consent.

Two original participant information and consent/assent forms must be completed, co-signed and dated personally by the participant if capable and by the person responsible for collecting the informed consent/assent.

If the parent(s)/legal representative are(is) unable to read, an impartial witness should be present during the entire informed consent discussion. The parent(s)/legal representative must give consent orally, and if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The participant's parent(s)/legal representative will be given one signed original information and consent form, and one original information and assent form. The second originals will be kept by the investigator.

A copy of the information and assent/consent form for the participant and his/her parent(s)/legal representative in the language(s) of the country is or are given in the "Participant information and consent form" document and in the "Parent(s)/Legal representative information and consent form" document attached to the protocol.

** Depending on the age of the minor, two different written information and consent forms may be prepared: one for the participant and one for his/her parent(s)/legal representative*

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IEC(s), and if applicable to the Competent Authorities.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IEC has been obtained and compliance with the local regulatory requirements, except for an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment and/or his/her parent(s)/legal representative must complete, date and co-sign one, or two if required by local regulation, original(s) of the new version of the information and consent form together with the person who collected the informed consent (and an independent witness, if applicable). He/She/They will receive one signed copy (or original, if required by local regulation) of the amendment to the information and consent form(s). The signed original(s) will be kept by the investigator

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CRF Part 11-compliant electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the participant's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the sponsor (e.g. documents relating to the IMP management…).
Data recorded directly on e-CRF and considered as source data (see section 4.6) must be collected immediately in the e-CRF. The other e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Inform software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.
Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed necessary via a request to the sponsor.

After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password.

After the data base lock, the investigator or an authorized member of his/her team will have to download from the e-CRF an electronic file containing participant data of his/her centre for archiving it in the study file (see section 14.3).

14.2. Data management

Data are collected via a CRF and stored in a secured database.

For data collected on the e-CRF, the Clinical Data Management of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from central laboratory, the Clinical Data Management of I.R.I.S. is responsible for data transfer. Centralised laboratory provide(s) electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Review Department of I.R.I.S. is responsible for data coding including:
- medical / surgical history, adverse events and procedures using MedDRA,
- medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

When data validation is achieved, a review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the IMP codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator or an authorized member of his/her team will download an electronic copy of each participant's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the study sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of I.R.I.S. The investigator commits himself not to publishing or communicating data collected in only one

centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. has been provided.

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, patient-level and/or study-level clinical trial data including clinical study reports (CSRs).

They can ask for all interventional clinical studies:

- submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the United States (US).
- Where Servier or an affiliate are the Marketing Authorization Holders (MAH). The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier's data sharing policy includes all interventional clinical studies in patients:

- sponsored by Servier,
- with a first patient enrolled as of 1 January 2004 onwards,

for New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any Marketing authorization (MA) approval

The datasets generated and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 6 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to

the IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, except for a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by Medical Writing Department in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and the coordinator must mutually agree on the final version. One copy of the final report must be dated and signed by the coordinator and the Director of the Center for Therapeutic Innovation.

The clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 6 months after the end of the clinical trial.

17.2. Concerning the sponsor

The sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the IMPs and the NIMPs administered during the study to enable him/her to carry out the study,
- supply the investigator with investigator's brochure if the IMP is not marketed,
- obtain any authorisation to perform the study and/or import licence for the IMPs administered that may be required by the local authorities before the beginning of the study,
- provide the coordinator annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IEC(s).
- take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non exhaustive):
  - Management of authorisation to access to personal data (e-CRF)
  - Identification and authentication measures before accessing personal data (e-CRF)
  - Traceability measures for the access to and modification of personal data (e-CRF)
  - Secured data transfer
  - Time limit for storing personal data
- handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to S95014 and study CL2-95014-002 are strictly confidential.
The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.
He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.
In case patient wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor (see Appendix 7).

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation (e.g. Food & Drug Administration 1572 form),
- to send, a copy of the IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible, in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

18. REFERENCES

Angiolillo AL, Schore RJ, Devidas M, Borowitz MJ, Carroll AJ, G astier-Foster JM, et al. Pharmacokinetic and pharmacodynamic properties of calaspargase pegol Escherichia coli L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: Results from Children´s Oncology Group Study AALL07P4. J Clin Oncol 2014; 32: 3874-82 [PE0150550]

Asselin BL. The three asparaginases: Comparative pharmacology and optimal use in childhood leukemia. Adv Exp Med Biol 1999a; 457: 621-629. [PE0150553]

Esparza SD, Sakamoto KM. Topics in pediatric leukemia—acute lymphoblastic leukemia. MedGenMed 2005;7:23 [PE0159181]

Heo YA et al. Pegaspargase: A Review in Acute Lymphoblastic Leukaemia. Drugs (2019) 79:767–777 [PE0153525]

Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl 5):v69–82. [PE0128919]

Kaprin, V. Starinsky, G. Petrova "Malignant neoplasms in Russia in 2018 (morbidity and mortality)", published in Moscow, 2019

Masetti R; Pession. A First-line treatment of acute lymphoblastic leukemia with pegasparaginase. Biologics. 2009; 3:359-368. [PE0151695]

National Comprehensive Cancer Network (NCCN). Acute Lymphoblastic Leukemia. 2020 [PE0159180]

Noone AM; Howlader N; Krapcho M; Miller D; Brest A; Yu M et al. 2018. SEER Cancer Statistics Review, 1975-2015 - Section 29: Childhood Cancer by the ICCC [PE0153306]

Silverman LB et al. Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia. Blood 2010;115:1351-1353 [PE0151917]

Tong WH, Pieters R, Kaspers GJ, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. Blood. 2014;123(13):2026–33. [PE0151923]

Van der Sluis IM et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica. 2016; 101(3):279-285. [PE0155838]

Vrooman LM et al. Efficacy and toxicity of pegaspargase and calaspargase pegol in childhood acute lymphoblastic leukemia/lymphoma: Results of DFCI 11-001. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 10006-10006 [PE0153989]

Other regulatory references:

ICH Topic E6 – Guideline for Good Clinical Practice: Consolidated guideline finalised (step 4) in June 1996. Adopted by CPMP, July 96, issued as CPMP/ICH/135/95/step 5, post step errata, July 2002.

ICH Topic E9 – Statistical Principles for Clinical Trials: Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96/step 5.

ICH Topic E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, issued as CPMP/ICH/377/95.

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), (2011/C 172/01)

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use.

Clinical Investigator's Brochure - ONCASPAR® (pegaspargase) (PEG-L-asparaginase, EZ-002, SHP 674) - Version n° 5 of 21 October 2020 [NP40790]

19. APPENDICES

Appendix 1: ALL-MB 2015 protocol

Appendix 2: NCCN guidelines 2020

Appendix 3: Patient performance status

Appendix 4: Hepatotoxicity form

Appendix 5: Trial Conduct During National or International Public Health Emergency

Appendix 6: World Medical Association Declaration of Helsinki

Appendix 7: Instructions to investigator for handling data rights requests