Statistical Analysis Plan

A Multicentre, Roll-over Study to Provide Continued Treatment With Lyophilized Pegaspargase (S95014) in Pediatric Patients With Acute Lymphoblastic Leukemia (ALL)

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List of abbreviations

ADA	:	Anti-Drug Antibodies
ADI	:	Actual dose intensity
AE	:	Adverse Event
AEOSI	:	Adverse Event Of Special Interest
ALL	:	Acute Lymphoblastic Leukemia
AST	:	Aspartate aminotransferase
BMI	:	Body Mass Index
BSA	:	Body Surface Area
CBI	:	Central Business Intelligence
CI	:	Confidence Interval
CTC	:	Common Terminology Criteria
CTCAE	:	Common Terminology Criteria for Adverse Events
ECG	:	ElectroCardioGram
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)
I.R.I.S.	:	Institut de Recherches Internationales Servier
IRS	:	Interactive Response System
MedDRA	:	Medical Dictionary for Regulatory Activities
NCI	:	National Cancer Institute
PEG	:	PolyEthylene Glycol
PDI	:	Planned dose intensity
PK	:	PharmacoKinetics
RDI	:	Relative Dose Intensity
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SAS	:	Safety Analysis Set
SD	:	Standard Deviation
TEAE	:	Treatment Emergent Adverse Event
TLG	:	Tables, Listings and Graphs
%CV	:	Coefficient of Variation in percent

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed, in accordance with the main characteristics of the study protocol v1.0, dated on December 2nd, 2020, the 1st non substantial Protocol Amendment, dated on May 5th, 2021, and the 2nd non substantial Protocol Amendment, dated on January 13th, 2022. The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

1.1. Study objectives

1.1.1. Primary objective

The main objective of this roll-over study is to provide continued access to S95014 during the consolidation phase in patients who completed the CL2-95014-002 study and who are clinically benefitting from S95014 without major toxicity.

1.1.2. Secondary objectives

Secondary objective of this roll-over study is to assess the safety profile of S95014 lyophilizate during the consolidation phase. All adverse events regardless of grade or causality and severity will be collected after the informed consent is signed and during the entire treatment period.

1.2. Study design

The present CL2-95014-003 study is a multicentre, non-randomized roll-over study of lyophilized Pegaspargase (Oncaspar®, S95014) formulation in the treatment of pediatric patients with ALL who completed the CL2-95014-002 study during the induction phase.

1.2.1. Study plan

Written informed consent and assent (when appropriate) will be obtained from each patient and/or his/her parent(s)/legal representative during the inclusion visit, corresponding to the withdrawal visit of the initial CL2-95014-002 study.

S95014 lyophilizate will be administered IV every two weeks during the consolidation phase at the dose of 1000, 2000 or 2500 U/m², as per investigator's judgment. Patients will be administered 9 infusions of S95014 lyophilizate, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27. Patients will receive other backbone chemotherapy agents as per ALL-MB 2015 protocol (see study protocol Appendix 1).

The study duration will be approximately 7 months, including the treatment period consisting of the consolidation phase and the follow-up period. After completing the consolidation phase, patient will be discontinued from the study and will be treated as per investigator's judgment.

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

- **Inclusion visit:** to obtain informed consent and check the inclusion/non-inclusion criteria. The inclusion visit of CL2-95014-003 study will correspond to the withdrawal visit of the initial CL2-95014-002 study.
- **Treatment period:** As per ALL-MB 2015 protocol, treatment period will start at Day 1 of the consolidation phase. Patients will be on treatment until the end of the consolidation

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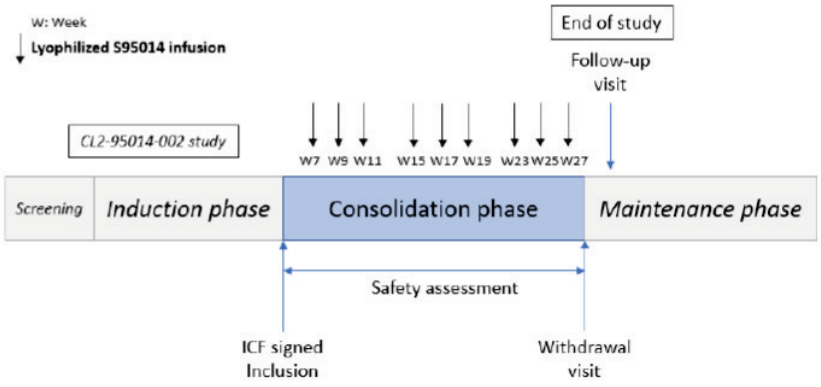
phase, unless they meet a discontinuation criterion as described in the Clinical Study Protocol.

- **Withdrawal visit:** no later than 30 days after the last dose of S95014 during the consolidation phase. Patient will continue receiving backbone chemotherapeutic regimen as per ALL-MB 2015 protocol, according to physician's judgment.
- **Follow-up visit:** should be made after Withdrawal visit, a contact or telephone call will be done not earlier than 30 days after the last S95014 infusion, except in case of consent withdrawal. Follow-up of adverse events and the patient's survival will be recorded.

The study plan is shown in Figure (1.2.1) 1.

Figure (1.2.1) 1 - Study plan



1.2.2. Type of randomisation

Not applicable.

1.3. Determination of sample size

The sample size was originally determined to provide sufficient statistical power to establish the PK comparability between the liquid and lyophilized formulations in the CL2-95014-002 study. After completing the CL2-95014-002 study, patients who agree to participate and meet the eligibility requirements will be included in this study. No further consideration is used to determine the sample size of this study.

2. ANALYSIS SETS / DOSE LEVEL

2.1. Analysis sets

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. The safety endpoints will be analyzed in the SAS. Unless otherwise stated, the safety analysis will be conducted in the overall SAS and by starting dose level if applicable.

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2.2. Investigational Medicinal Product (IMP) and dose level

S95014 lyophilizate is considered as IMP.

S95014 dosage is calculated according to body surface area (BSA). The BSA will be manually calculated by the investigator based on the height and weight measured on the day of S95014 infusion (all BSA calculations are rounded to 2 decimal places).

S95014 lyophilizate will be administered IV, over 1 to 2 hours, every two weeks during the consolidation phase at the dose of 1000, 2000 or 2500 U/m², as per investigator's judgment. Patients will be administered 9 infusions of S95014 lyophilizate, at week 7, 9, 11, 15, 17, 19, 23, 25 and 27. Patients will receive other backbone chemotherapy agents as per ALL-MB 2015 protocol.

3. STATISTICAL METHODS

3.1. General considerations

All data processing, summarization, and analyses will utilize SAS® software package, Version 9.4, unless otherwise specified.

3.1.1. Descriptive statistics

For **qualitative data**, number of observed values, number and percentage of subjects per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.

For **quantitative data**, number of observed values, mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented.

3.1.2. General definitions

Unless specified otherwise in section 3.3 to 3.5, the following definitions will be considered:

- Analysable value will be defined as any non-missing value.
- Baseline value will be defined as the last analysable value prior to the first IMP intake in CL2-95014-002 study (i.e. before or the same date as the first IMP intake date).
- Post-baseline value will be defined as any value recorded at a given timepoint after baseline.
- Change from baseline will be defined as the arithmetic difference between a post-baseline value and the baseline value for a given variable at a given time point.

3.2. Handling of Missing, Unused, and Spurious Data

No specific imputation method will be used for missing data, unless otherwise specified.

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:

[redacted]

- 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).

Missing dates

If no specific management of dates is defined, missing information is substituted as shown below:

Table (3.1.2) 1 - Substitution rules of dates if no specific management is defined

Date to substitute		Substituted date
Date	../mmm/yyyy	01/mmm/yyyy
	../…./yyyy	01/JAN/yyyy
	../…./….	No substitution

Note:
../mmm/yyyy = missing day
../…./ yyyy = missing day and month
../…./…. = missing date

3.3. Disposition and baseline characteristics

Disposition of subjects and baseline characteristics will be described overall and by starting dose level, if applicable, to assess their comparability.

3.3.1. Disposition of subjects

Subject disposition will be tabulated for all subjects by summarizing the number and percentage of subjects completed study treatment, discontinued from the study and by the primary reason for discontinuation, who are included in the SAS overall and by starting dose level, if applicable.

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

3.3.2. Protocol deviations

Important protocol deviations will be summarized in the overall SAS and by starting dose level if applicable, using the number and percentage of subjects who had each type of deviation for the SAS. COVID-19 related protocol deviation will be also summarized. Protocol deviations will be reviewed by the sponsor prior to the database lock. In addition, these protocol deviations will be listed:

- Inclusion/Exclusion criteria not respected
- Study Withdrawal criteria not respected
- Safety/Rights affected

[redacted]

3.3.3. Demographic data and other baseline characteristics

Demographic and baseline measurements will be summarized for the SAS, 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. For this purpose, data of the CL2-95014-002 study may be used.

The following baseline characteristics will be summarized based on descriptive statistics:

- Age at inclusion (years; if not available, then it will be calculated as the biggest integer <= [(ICF date – date of birth + 1) / 365.25])
    - As continuous variable
    - By Age Category I (age <10, 10 - <16, and >= 16 years)
    - By Age Category II, EudraCT categories (0-27 days, 27 days-23 months, 2-11 years, 12-17 years, 18-65 years, >= 66 years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI (kg/m^2) = weight (kg) / height (m^2))
- Body Surface Area (BSA(m^2) = sqrt (height (cm) x weight (kg) / 3600))

3.4. Treatments of subjects

3.4.1. Extent of exposure

The SAS will be used for exposure unless otherwise specified. Exposure to S95014 lyophilizate for each subject will be listed. The following metrics will be summarized:

- Duration of treatment (months): (last date of study drug − first date of study drug + 1)/ 30.4375
- Number of doses administered: total number of S95014 infusions
- Cumulative actual dose (U/m^2): total dose of study drug infused to a patient in the study
- Actual dose intensity (ADI, $U/(m^2 \times month)$): cumulative actual dose (U/m^2) / duration of treatment (months)

[redacted]

- Planned dose intensity (PDI, U/(m^2×month)): cumulative planned dose (U/m^2) / duration of treatment (months), where cumulative planned dose = planned number of S95014 infusions × starting dose
- Relative dose intensity (RDI): ADI (U/m^2×month)/PDI (U/(m^2×month))

Listing of all dose change/interruption and reasons will be produced.

3.4.2. Concomitant treatments

Concomitant medication for each subject in the SAS will be listed.

3.5. Safety analysis

All subjects included in the safety analyses will be evaluated overall and by the starting dose level if applicable, unless otherwise specified.

3.5.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence in a subject who received IMP (S95014), which occurs within the period from the Inclusion visit, until 30 days after the last S95014 infusion, or the date of withdrawal, whichever is earlier. TEAE will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria Adverse Events (CTCAE) v5.0. Clinically significant laboratory abnormalities will be classified into Common Terminology Criteria (CTC) grade according to CTCAE v5.0 and will be reported as adverse events if they are associated with signs and symptoms or, clinically significant in the investigator's opinion except if related to the disease, if they require curative therapies, if they induce change of study treatment administration All analyses described below will be based on TEAEs, if not otherwise specified.

Adverse events will be summarized in hierarchical tables, presenting the number and percentage of subjects 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 treatment 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, starting dose level if applicable and, in some case, worst 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 AEs 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.

3.5.2. Other Safety Evaluations

Descriptive statistics of laboratory parameters and continuous variables of vital signs will be calculated for each time point. Shift tables for qualitative urinalysis results at each time point after the first IMP infusion will be created. Height, weight, BSA and BMI will be summarized by visit.

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 CTCAE v5.0 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. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

4. INTERIM ANALYSIS

No interim analysis is planned for this study.

5. APPENDICES

Not applicable.

6. CHANGES FROM THE PLANNED STATISTICAL ANALYSIS

Not applicable.

7. REFERENCES

Not applicable.