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Reason for signing: Approved	Name: PPD Role: B Date of signature: 12-Jun-2025 21:29:13 GMT+0000

Reason for signing: Approved	Name: PPD Role: B Date of signature: 12-Jun-2025 21:57:47 GMT+0000

Reason for signing: Approved	PPD Date of signature: 13-Jun-2025 17:58:28 GMT+0000

Signature Page for VV-TMF-260226 v1.0

Protocol code (11 or 12 c) - Statistical Analysis Plan (analysis period, if applicable) - Working version X.Y or Final version X.00

SERVIER BIO-INNOVATION

Document title	**STATISTICAL ANALYSIS PLAN (SAP): STUDY CL2-95015-001**
Full title	*SPARK-ALL: A Multi-center, Open-label, Single-arm Phase 2/3 Trial Evaluating the Safety and Pharmacokinetics of Calaspargase Pegol for Treatment of Adults Aged 22 To > 65 Years with Newly-diagnosed Philadelphia-negative ALL*
Short title	*SPARK-ALL: Calaspargase Pegol in Adults with Untreated, Ph-negative B-cell and T-cell ALL*
Test drug code	*Calaspargase pegol-mknl (Asparlas, S95015)*
Indication	*Asparlas (calaspargase pegol) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia*
Development phase	*2/3*
Sponsor	*Institut de Recherches Internationales Servier (I.R.I.S.)* *22, route 128, 91190 Gif-sur-Yvette – France*
Investigational New Drug application umber	*100594*
Date of the document	*4 June 2025*
Version of the document	*1.0*

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Follow up of versions

Version	Release date (dd/mm/yyyy)	Key change(s) (*)	Protocol version associated	Rationale
1.0	04/06/2025	See section 7	Protocol v7.0	Original version

(*) Key changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Key changes from the previous signed version for the other SAP signed version(s). See also section 7 for the changes to protocol-planned analyses.

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List of abbreviations

ADA	anti-drug antibody
ADI	actual dose intensity
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the plasma asparaginase activity-time curve
aPTT	activated partial thromboplastin time
BLQ	below the LLOQ
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum observed plasma asparaginase activity
CNS	central nervous system
CR	complete remission
CRF	case report form
CTC	Common Terminology Criteria
DBP	diastolic blood pressure
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
eCRF	electronic case report form
FAS	full analysis set
FISH	fluorescence situ hybridization
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
I.R.I.S.	Institut de Recherches Internationales Servier
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NPAA	nadir plasma asparaginase activity
OS	overall survival
PAA	plasma asparaginase activity
PD	pharmacodynamic
PDI	planned dose intensity
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PS	performance status

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PT	preferred term
PT-INR	prothrombin time and international normalized ratio
RBC	red blood cells
RDI	relative dose intensity
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse event
TLG	tables, listings and graphs
UT	unacceptable toxicity
WBC	white blood cells
WHO	World Health Organization

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1. INTRODUCTION

This Statistical Analysis Plan details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol version 7.0 dated from 30 October 2024. The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

1.1. Study objectives and endpoints

1.1.1. Primary Objectives

Part 1:
To confirm the recommended doses for Part 2 using safety and plasma asparaginase activity data (PAA) in the 4 different groups:

- Young adults aged 22 to 39 years and body mass index (BMI) ≤ 35 kg/m^2.
- Adults aged 40 to < 55 years and BMI ≤ 35 kg/m^2.
- Adults aged ≥ 55 years and BMI ≤ 35 kg/m^2.
- Adults aged < 55 years and BMI > 35 kg/m^2.

Part 2:

- To evaluate the nadir plasma asparaginase activity (NPAA) as a surrogate for efficacy (NPAA level ≥0.1 U/mL 21 days after the consolidation Day 43 dose).
- To evaluate the safety profile of calaspargase pegol through the occurrence of treatment-emergent adverse events (TEAEs), including adverse events of special interest (AESIs).

1.1.2. Secondary Objectives

Part 1:

- To evaluate the efficacy of calaspargase pegol when combined with multi-agent chemotherapy.
- To evaluate the PK of calaspargase pegol.
- To evaluate the immunogenicity (anti-drug antibody [ADA] and anti-PEG development).

Part 2:

- To evaluate the efficacy of calaspargase pegol when combined with multi-agent chemotherapy.
- To evaluate PAA level at pre-defined time points during induction and post-induction, respectively.
- To evaluate the PK of calaspargase pegol.
- To evaluate the immunogenicity (ADA and anti-PEG development).

1.1.3. Exploratory Objectives

- To evaluate MRD status at the end of the consolidation phase.
- To explore for molecular biomarkers that may be indicative of clinical response/resistance.

1.1.4. Endpoints

The study endpoints for Part 1 and Part 2 are listed in Table 1 and Table 2, respectively.

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Table 1 - Part 1 Objectives and Endpoints

Tier	Objective(s)	Endpoint(s)
Primary	To confirm the recommended doses for Part 2 using safety and PK/PD data in different age groups	- Incidence of unacceptable toxicities after the induction Day 4 dose within the evaluation period - Global safety assessment using incidence of AEs and SAEs; laboratory tests (hematology, biochemistry, coagulation, liver function tests); vital signs - PK/PD (PAA)
Secondary	Efficacy	- MRD negative status at the end of induction - CR - 1-year EFS, DFS, and OS - 2-year EFS, DFS, and OS - 3-year EFS, DFS, and OS
	PK	PAA-derived PK parameters (*e.g.*, C_{max}, AUC)
	Immunogenicity	Anti-drug antibodies (ADA)
Exploratory	Consolidation MRD	End-consolidation MRD status for subjects who are MRD positive at the end of the induction phase
	Biomarkers	Glutamine and derivatives

ADA = anti-drug antibody; AE = adverse event; AUC = area under the plasma asparaginase activity-time curve; C_{max} = maximum observed plasma asparaginase activity; CR = complete remission; DFS = disease-free survival; EFS = event-free survival; MRD = minimal residual disease; OS = overall survival; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event

Table 2 - Part 2 Objectives and Endpoints

Tier	Objective(s)	Endpoint(s)
Primary	Evaluate the safety of calaspargase pegol in adults	Incidence of AEs with focus on asparaginase class toxicities; laboratory tests (hematology, biochemistry, coagulation, liver function tests); physical examination, and vital signs
	PD (NPAA)	NPAA[1] ≥ 0.1 U/mL 21 days after the consolidation Day 43 dose
Secondary	PD (PAA)	- PAA level ≥ 0.1 U/mL at any time during induction and post-induction, respectively - PAA level ≥ 0.025, ≥ 0.1, ≥ 0.2, or ≥ 0.4 U/mL at predefined time points during induction and post-induction, respectively
	PK	PAA-derived PK parameters (*e.g.*, C_{max}, AUC)
	Efficacy	- MRD negative status at the end of induction - CR - 1-year EFS, DFS and OS - 2-year EFS, DFS and OS - 3-year EFS, DFS and OS
	Immunogenicity	Anti-drug antibodies (ADA)
Exploratory	Consolidation MRD	End-consolidation MRD status for subjects who are MRD positive at the end of the induction phase
	Biomarkers	To explore for molecular biomarkers that may be indicative of clinical response/resistance

ADA = anti-drug antibody; AE = adverse event; AUC = area under the plasma asparaginase activity-time curve; C_{max} = maximum observed plasma asparaginase activity; CR = complete remission; DFS = disease-free survival; EFS = event-free survival; MRD = minimal residual disease; OS = overall survival; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event

[1]NPAA is defined as the target durable day 21 time point post-administration of calaspargase pegol.

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1.2. Study design

This is a multi-center, open-label, single-arm study of calaspargase pegol for the treatment of newly diagnosed Philadelphia-negative ALL in adults aged ≥ 22 years, including adults aged > 65 years. The study is being conducted to assess calaspargase pegol safety, tolerability, PK, PD, and anti-leukemic activity in adults.

1.2.1. Study plan

The study will be conducted in 2 parts (Figure 1). Part 1 is a dose confirmation run-in period to evaluate the safety of calaspargase pegol administration and obtain PAA data for the proposed calaspargase pegol doses in each patient group. Calaspargase pegol dose will be based on the patients' age and BMI. The starting doses for each patient group are based on the recommendations of the Scientific Advisory Board with expertise in treatment of adults with ALL. Historically higher rates of certain asparaginase-class toxicities have been observed with increasing age, particularly in older and obese adults with ALL. Older patients and those with high BMI will therefore receive a lower starting dose relative to the younger, non-obese adults. There are four patient groups defined in Part 1:

- Young adults aged 22 to 39 years and body mass index (BMI) ≤ 35 kg/m^2.
- Adults aged 40 to < 55 years and BMI ≤ 35 kg/m^2.
- Adults aged ≥ 55 years and BMI ≤ 35 kg/m^2.
- Adults aged < 55 years and BMI > 35 kg/m^2.

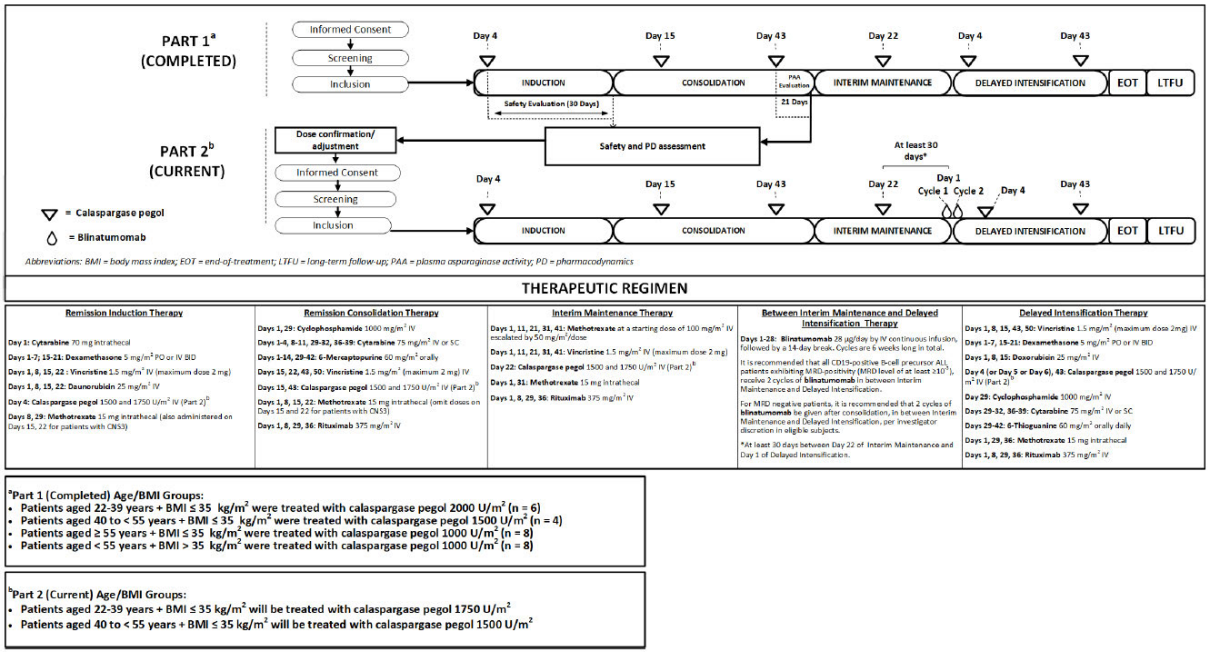
Based on the findings of the required Part 1 safety and PAA data, for Part 2, no additional enrollment of patients ≥ 55 years or those with BMI > 35 kg/m2 will take place; and patients will be treated as follows:

- Patients aged 22 to 39 years + BMI ≤ 35kg/m2 will be treated with calaspargase pegol 1750 U/m2 (dose reduced from 2000 U/m2 in Part 1).
- Patients aged 40 to < 55 years + BMI ≤ 35kg/m2 will be treated with calaspargase pegol 1500 U/m2 (unchanged from Part 1).

It is to be noted that, patients whose BMI increases to > 35 kg/m2 or whose age increases to >55 years during the course of the study, may continue their participation in the study and dosing will be based on what was assigned at initial enrollment. It will be at the investigator's discretion to also take into account risk factors and comorbidities for each of these patients.

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Figure 1 - Study plan



1.2.2. Type of randomization

Not applicable.

1.3. Determination of sample size

Part 1 is a dose confirmation phase. Approximately 4-8 patients will be enrolled for each patient group in part 1.

The number of patients treated at the recommended doses (Part 1 and Part 2 combined) in the combined patient groups (aged 22 to 39 years and BMI ≤ 35 kg/m² + aged 40 to < 55 years and BMI ≤ 35 kg/m²) is determined to provide at least 90% power for the lower bound of the 95% CI of the proportion of evaluable patients achieving the target NPAA level for the primary NPAA endpoint (i.e., PAA at 21 days after the Consolidation Day 43 dose ≥ 0.1 U/mL) to be above a threshold. It is predicted based on PK modeling and simulation that approximately 97% of the patients treated with 1750 U/m^2 and 1500 U/m^2 will achieve the target NPAA level.

Using this 97% as the true proportion of evaluable patients achieving the target NPAA level for the combined patient groups (aged 22 to 39 years and BMI ≤ 35 kg/m² + aged 40 to < 55 years and BMI ≤ 35 kg/m²) treated at the recommended dose levels, and a corresponding threshold of 85% for the 95% CI lower bound, a minimum of 56 evaluable patients treated at the recommended doses are required to provide at least 90% power.

At the end of the Part 1, the recommended dose is 1750 U/m^2 for patients aged 22 to 39 years and BMI ≤ 35 kg/m², and 1500 U/m^2 for patients aged 40 to < 55 years and BMI ≤ 35 kg/m². Two subjects from the 1500 U/m^2 group in Part 1 were evaluable for NPAA to be included in the Primary Nadir Plasma Asparaginase Activity Analysis Set.

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The historical estimate of the incidence rate for Grade ≥ 3 hyperbilirubinemia, any grade thrombosis, Grade ≥ 3 pancreatitis, and Grade ≥ 3 hypersensitivity are 27.7%, 18.4%, 7.5%, and 16.6%, respectively. Assuming a 10% increase is observed in each adverse event of special interest (AESI), given 60 patients, the Clopper-Pearson CI of each observed AESI rate is shown in the following Table 3. For each AESI, the historical incidence rate is excluded by the lower bound of Clopper-Pearson CI of the observed rate. Thus, a total of 60 patients may be sufficient to exclude a clinical meaningful increase in each AESI.

Table 3 - Sample Size Justification for Safety Analysis

Adverse Event of Special Interest	Incidence Rate: Historical Estimate	Observed Incidence Rate Assuming 10% Increase	80% Clopper-Pearson Confidence Interval of Observed Incidence Rate Given 60 Patients
Grade ≥3 hyperbilirubinemia	27.7%	37.7%	(29.3%, 46.8%)
Any grade thrombosis	18.4%	28.4%	(20.8%, 37.2%)
Grade ≥3 pancreatitis	7.5%	17.5%	(11.3%, 25.4%)
Grade ≥3 hypersensitivity	16.6%	26.6%	(19.2%, 35.3%)

The study will stop enrollment when 56 patients are evaluable for NPAA and a minimum of 60 patients are evaluable for safety.

2. STATISTICAL HYPOTHESES AND MULTIPLICITY HANDLING

2.1. Statistical hypotheses

Not applicable.

2.2. Multiplicity handling

Not applicable.

3. ANALYSIS SETS / TREATMENT GROUPS

3.1. Analysis sets

3.1.1. Full Analysis Set

The full analysis set (FAS) will include all subjects who received at least 1 administration of study medication calaspargase pegol. The FAS will be used for all safety analyses, including AEs, exposure to study treatment, concomitant medications and other safety data. Secondary efficacy analyses will also be conducted using the FAS.

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3.1.2. Primary NPAA Analysis Set

The primary NPAA (PNPAA) endpoint refers to the PAA 21 days after the consolidation Day 43 dose. The PNPAA analysis set (PAS) will include all evaluable subjects in Part 1 and Part 2 in the combined patient groups (aged 22-39 years and BMI ≤ 35 kg/m²+aged 40-54 years and BMI ≤ 35 kg/m²) who are treated at the recommended dose level.

Subjects will not be evaluable for the PNPAA analysis if they

- Received at least one dose different from the corresponding recommended Part 2 dose level before and including the consolidation Day 43 dose,
- Did not receive all scheduled doses before and including the consolidation Day 43 dose.
- Had non-evaluable or missing PAA sample 21 days after the consolidation Day 43 dose.
- Developed anti-drug antibodies (ADA) before the consolidation Day 43 dose
- Had any other factors that may impact the interpretability of the PNPAA analysis.
- Developed silent inactivation on or before day 21 after consolidation Day 43 dose.

3.1.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) will include all subjects who have received at least 1 dose of calaspargase pegol and are evaluable for PK analysis. The PK dataset will include only the subjects who had sufficient samples collected to provide interpretable PK results with no deviations that might have affected the PK interpretation.

3.1.4. Immunogenicity Analysis Set

The immunogenicity analysis set (IGAS) will include all subjects who have received at least 1 dose of calaspargase pegol and have at least 1 post-dose sample evaluable for immunogenicity testing.

3.2. Treatment groups

Calaspargase pegol (2000 U/m^2, 1750 U/m^2, 1500 U/m^2, 1000 U/m^2) were administered based on study part, age and BMI (Table 4 and Table 5).

Table 4 - Calaspargase pegol Starting Doses for Part 1

Patient groups	**Calaspargase pegol starting doses**
Adults aged 22-39 years and BMI ≤ 35 kg/m2	2000 U/m^2
Adults aged 40 to < 55 years and BMI ≤ 35 kg/m2	1500 U/m^2
Adults aged ≥ 55 years and BMI ≤ 35 kg/m2	1000 U/m^2
Adults aged < 55 years and BMI > 35 kg/m2	

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Table 5 - Calaspargase pegol Doses for Part 2

Patient groups	**Calaspargase pegol starting doses**
Adults aged 22-39 years and BMI ≤ 35 kg/m2	1750 U/m^2
Adults aged 40 to < 55 years and BMI ≤ 35 kg/m2	1500 U/m^2

4. GENERAL STATISTICAL CONSIDERATIONS

Unless otherwise specified, all analyses will be conducted by patient group and dose level if estimable.

Unscheduled visits after first dosing date will not be included in summary statistics, except for the baseline derivation and the shift table of worst post-baseline laboratory values. SAS version 9.4 or higher will be used.

4.1. Descriptive statistics

For quantitative data, number of observed values, mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented. The geometric mean will also be provided for log-distributed data (if applicable).

Categorical data will be summarized using frequencies and percentages.

For event data, the following will be presented:

- number of patients having experienced the event (n)
- number of patients at risk for the event (N)
- global incidence rate (%) calculated as the ratio between the number of patients having experienced the event (n) and the number of patients at risk at the beginning of the study (N).

4.2. General definitions

4.2.1. Definition of baseline

Unless otherwise specified, the baseline value for safety endpoints is defined as the last non-missing value on or prior to first study drug administration date/time. Unless otherwise specified, assessments or procedures planned before the first dose of the study drug per protocol, will be assumed pre-dose if conducted on the same day as the first study drug administration. Unscheduled visits will be considered in baseline derivation.

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4.2.2. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings, and partial and missing data will be clearly indicated as missing.

- Handling of unknown causality assessment for AE:
    - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related".
- Handling of missing severity grades for AE:
    - The missing severity will be imputed by the maximum severity on the remaining AEs under the same PT and same patient. If the severity is missing for all the occurrences or the PT is missing, then it will be classified as "missing".
- Handling of missing/partial dates for AEs or concomitant medications:
    - In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date does not indicate whether the AE started prior to or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.
    - These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.
- Handling of missing baseline for immunogenicity:
    - Missing baseline ADA results will be imputed as negative.

5. STATISTICAL ANALYSES

5.1. Study patients

5.1.1. Disposition

Subject disposition will be tabulated by summarizing the number and percentage of subjects who are included in the FAS, completed study treatment, who are ongoing for the study drug treatment, discontinued from the study treatment overall and by treatment phase, and the primary reason for discontinuation.

Duration of follow-up (from last study drug dosing date to last follow-up date) in months will also be summarized. The end of study status will also be summarized with the following categories: "On study" or "Discontinued". The discontinued subjects will be classified by the

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earliest date of withdraw consent from treatment and follow-up, death, lost to follow up or complete follow-up.

Patients who completed all study drug doses are considered completing study treatment.

A subject data listing will present date, phase, study day, and reason of study treatment discontinuation, date of study discontinuation and the primary reason, for the FAS.

5.1.2. Protocol Deviations

Important protocol deviations will be summarized based on the FAS. The important deviations will be identified and finalized as such, after the team review, before the database lock.

A by-subject listing with all important protocol deviations will be provided for subjects in the FAS.

5.1.3. Demographic data and baseline characteristics

5.1.3.1. Demographics and physical measurements

Demographic characteristics and physical measurements at baseline will be summarized in the FAS as follows. By-subject data listings will also be provided.

- Demographic characteristics
  - Age (years): summary statistics
  - Sex: Male, Female
  - Race: White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other, Not Reported
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported
- Physical measurements
  - Baseline Height (cm)
  - Baseline Weight (kg)
  - Baseline BMI (kg/m^2)
  - Baseline BSA (m^2)

5.1.3.2. Baseline characteristics

The following baseline characteristics of the underlying disease will be summarized in the FAS. By-subject data listings will also be provided.

- White blood cells (WBC) count (x10^9/L): summary statistics
- White blood cells (WBC) count (x10^9/L) categories:
  - <50, ≥ 50
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at baseline (0, 1, or 2)

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- CNS status
- Immunophenotype (Note: Data collected under "Staging at diagnosis" in the CRF)
- FISH mutation
- Cytogenetics

Medical history other than ALL will be summarized by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who had at least one occurrence of an event (PT) within an SOC. The summary will be sorted alphabetically by SOC and by decreasing frequency of PTs within an SOC. Medical history of ALL will be summarized. Listing of medical history will be provided.

5.2. Treatment of patients

5.2.1. Extent of exposure and treatment compliance

Duration of exposure in months, cumulative dose (U and U/m^2), relative dose intensity (RDI), actual dose intensity (ADI), planned dose intensity (PDI), number and percentage of patients with a dose reduction, dose interruption and dose delay, duration of dose delay in days, total number of doses administered and percentage with target number of doses administered will be summarized for the FAS with definitions as below:

- Duration of exposure (months): (last date of study drug − first date of study drug+21)/ 30.4375
- Cumulative dose (U, U/m^2): total dose of study drug taken by a patient in the study
- ADI (U/m^2.month): cumulative dose (U/m^2) / duration of exposure (months)
- PDI (U/m^2.month): cumulative planned dose (U/m^2) / duration of exposure (months)
- RDI (%): 100 × ADI (U/m^2.month) / PDI (U/m^2.month)
- Total number of doses administered: total number of non-zero doses of study drug taken by a patient in the study.
- % with target number of doses administered: 100 × total number of doses administered/the target number of doses planned.

Note: Calaspargase pegol will be administered at Day 4 (or 5, or 6) of the induction phase, Days 15 and 43 of the consolidation phase, Day 22 of the interim maintenance phase and Days 4 (or 5, or 6) and 43 of the delayed intensification phase. Thus, the target number of dose is 6.

Duration of dose delay will be calculated based on the actual dose date and the planned dose date, specifically:

- actual dose date - earliest date of dexamethasone, vincristine or daunorubicin – 5, if the delay happens at the 1st dose
- actual dose date – consolidation Day 1 date – 15+1, if the consolidation Day 15 dose is delayed
- actual dose date – consolidation Day 1 date – 43+1, if the consolidation Day 43 dose is delayed
- actual dose date – interim maintenance Day 1 date – 22+1, if the interim maintenance Day 22 dose is delayed

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- actual dose date – delayed intensification Day 1 date – 4+1, if the delayed intensification Day 4 dose is delayed
- actual dose date – delayed intensification Day 1 date – 43+1, if the delayed intensification Day 43 dose is delayed

The date of "Day 1" for consolidation, interim maintenance, and delayed intensification phases are defined as below:

- Day 1 of consolidation: first date of cyclophosphamide, cytarabine or 6-mercaptopurine that was administered during consolidation phase.
- Day 1 of interim maintenance: first date of vincristine or methotrexate that was administered during interim maintenance phase.
- Day 1 of delayed intensification: first date of vincristine, dexamethasone, or doxorubicin that was administered during delayed intensification phase.

Subject data listing of exposure and compliance to the study drug including start/end dates, dose, complete dose as planned, action taken and reason for action taken will be provided for the FAS.

5.2.2. Previous and Concomitant treatments

The following summaries will be presented by patient group and dose level based on the FAS.

Previous treatments are any treatments received by the patient prior to the first dose of study treatment. Previous treatments can be discontinued before first dose of study treatment or can be ongoing during treatment period.

Concomitant treatments are defined as non-study medications that are started on or after the first dose date; or are started before the start of the study treatment and end or remain ongoing during the treatment period.

All non-study medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE). All concomitant medications will be summarized in frequency tabulations according to ATC code into 4 levels (pharmacological class, pharmacological sub-class, therapeutic class, preferred name) and 1 level (pharmacological class). The summaries will include concomitant treatments at the first IMP (Calaspargase pegol) infusion; and during the treatment period. Listing of previous and concomitant treatments will be provided.

A patient taking the same medication multiple times will only be counted once.

5.3. Efficacy analysis

5.3.1. Efficacy endpoints

Efficacy endpoints for patients will be summarized by each patient group, dose level, including the combined patient groups (aged 22-39 years and BMI $\leq$ 35 kg/m² + aged 40-54 years and BMI $\leq$ 35 kg/m²) who are treated at the recommended dose level, in the FAS. By-subject data listings will also be provided.

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5.3.1.1. Complete Remission (CR)

Complete remission is achieved when patients achieve complete response (including complete response with incomplete blood count recovery) for blood and bone marrow, remission for CNS disease, and complete response for lymphomatous extramedullary disease. The number and proportion of patients achieving CR will be summarized.

5.3.1.2. Minimal Residual Disease (MRD)

The frequency and proportion of MRD status and bone marrow results will be summarized by visit. A 2-sided 95% Clopper-Pearson CI of negative MRD status will be presented by visit. MRD and bone marrow results will be performed and summarized using local and central data separately.

5.3.1.3. Event-free Survival (EFS)

Event-free survival is defined as time from the first dose of calaspargase pegol to the date of induction failure (positive MRD or failure to achieve CR at end-of-induction assessment), documented relapse, diagnosis of a second malignant neoplasm (including myelodysplastic syndrome), or death from any cause, whichever comes first. In the absence of a documented EFS event as defined above, EFS is to be censored on the date of last evaluation.

If a patient starts new anti-cancer therapy, including asparaginase Erwinia substitution, without EFS events, the EFS will be censored at the start date of new anti-cancer therapy.

The quartiles and median of the EFS will be estimated along with the 95% CIs using the log-log transformation method. A summary and a plot of the Kaplan-Meier estimates of the EFS will be provided along with the number at risk. The EFS rate at 1 year, 2 years and 3 years after the first dose of calaspargase pegol will be calculated along with the 95% CIs estimated using the Kaplan-Meier method, respectively.

5.3.1.4. Disease-free Survival (DFS)

Disease-free survival is defined as time from achievement of CR to the documented relapse, diagnosis of a second malignant neoplasm or death for subjects who achieve a CR. The same analysis and censoring rules for EFS will be applied to DFS.

The quartiles and median of the DFS will be estimated along with the 95% CIs using the log-log transformation method. A summary and a plot of the Kaplan-Meier estimates of the DFS will be provided along with the number at risk. The DFS rate at 1 year, 2 years and 3 years after the first dose of calaspargase pegol will be calculated along with the 95% CIs estimated using the Kaplan-Meier method, respectively.

5.3.1.5. Overall Survival (OS)

Overall survival is defined as time from the first dose of calaspargase pegol to death from any cause. If the subject is alive at the date of the analysis, then OS will be censored at the last contact date.

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The quartiles and median of the OS will be estimated along with the 95% CIs using the log-log transformation method. A summary and a plot of the Kaplan-Meier estimates of the OS will be provided along with the number at risk. The OS rate at 1 year, 2 years and 3 years after the first dose of calaspargase pegol will be calculated along with the 95% CIs estimated using the Kaplan-Meier method, respectively.

5.4. Safety analysis

Safety for patients will be summarized by each patient group, dose level, and the combined patient groups (aged 22-39 years and BMI $\leq$ 35 kg/m^2 + aged 40-54 years and BMI $\leq$ 35 kg/m^2) who are treated at the recommended dose level, and overall in the FAS.

5.4.1. Adverse events

Treatment-emergent AEs will be assessed according to the CTCAE v5.0. A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence in a patient who received calaspargase pegol, which occurs within the period from the first dose of study drug to 30 days after the last dose of study drug in the study. Laboratory abnormalities will be classified into Common Terminology Criteria (CTC) grade according to CTCAE v5.0 and will be reported as AEs.

All TEAEs will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

A safety overview will be presented by patient group and dose level for the FAS and will include the number and percentage of subjects with at least one:

- Any TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death
- Treatment-related TEAEs
- Treatment-related Grade 3/4 TEAEs
- Treatment-related Serious TEAEs
- Treatment-related TEAEs leading to discontinuation of study drug
- Treatment-related TEAEs leading to death

The following summaries will be presented in separate tables by System Organ Class and Preferred Term for the FAS:

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- TEAEs regardless of study drug relationship
- Grade 3/4 TEAEs
- Treatment-related TEAEs
- Treatment-related Grade 3/4 TEAEs
- TEAEs leading to discontinuation of study drug
- Serious TEAEs
- Treatment-related Serious TEAEs
- Serious TEAEs leading to discontinuation of study drug

A subject reporting the same event more than once will be counted once when reporting the number of subjects with that particular event.

By-subject data listings will also be provided for the following: all TEAEs; serious TEAEs; and subject deaths; and any other information collected (e.g., start/end dates and duration of AE, seriousness, severity, or relatedness to study drug) will be listed as appropriate.

AEs of special interest will be analysed separately. Any such events will be identified prior to database lock. The frequency and proportion with a 2-sided 80% Clopper-Pearson CI of each AESI will be summarized. For calaspargase pegol, AESI include:

- Grade ≥ 3 ALT/AST increase or Grade ≥ 3 hyperbilirubinemia.
- Grade ≥ 3 hemorrhage and all thromboembolic events regardless of the grade, excluding catheter-related events.
- Grade ≥ 3 pancreatitis.
- Grade ≥ 3 hypersensitivity/infusion reactions per CTCAE v5.0.

The registrational trial DFCI 11-001 for Asparlas reported 80% CI of the AE in the pediatric population; therefore 80% CI is chosen to ensure consistency in reporting the descriptive summary of AE incidence.

5.4.2. Clinical laboratory evaluation

Unless specified otherwise, lab data will be summarized by patient group and dose level in scheduled visits.

For each laboratory parameters, the actual values and the change from baseline will be summarized.

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Shift tables from baseline to worst value based on CTCAE grade (using separate CTCAE term for both directions of CTCAE grading, low and high, as applicable). The laboratory data will be presented by patient group and dose level, including:

- Hematology tests including Hematocrit, Hemoglobin, RBCs, WBCs, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts in absolute value and in %)

- Biochemistry tests including Total Protein, Albumin, ALP, ALT, AST, GGT, Ammonia, Bicarbonate, LDH, Calcium and Corrected Calcium, Phosphate, Sodium, Potassium, Serum Creatinine, Creatinine Clearance, Direct Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Triglycerides, BUN, Uric Acid, Amylase, Lipase, Glucose

- Coagulation tests including PT-INR, Fibrinogen, Protein S Activity, aPTT, D-dimer

5.4.3. Vital signs, clinical examination and other observations related to safety

5.4.3.1. Vital signs and clinical examination

The following vital signs will be analysed:

- Weight (kg)
- SBP (mmHg)
- DBP (mmHg)
- Heart rate
- Temperature

They will be described, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to each post baseline visit under treatment. Vital sign measurements will also be listed.

The following clinical examination will be listed:

- FISH
- Cytogenetics
- Immunophenotyping
- Testicular involvement

5.5. Quality of Life

Not applicable.

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5.6. Exploratory analysis

The frequency and proportion with end-consolidation MRD will be summarized for subjects who are MRD positive at the end of the induction phase.

5.7. Pharmacokinetic and Pharmacodynamic Analyses

5.7.1. Pharmacokinetic/Pharmacodynamics Interpretation of Asparaginase Activity

All PK/PD interpretations will be performed at I.R.I.S. under the responsibility of the Quantitative Pharmacology department. The PK analysis set will include all patients who have received at least 1 calaspargase pegol dose and are evaluable for PK with no deviation that might affect the analysis. Assessments for PK/PD and therapeutic drug monitoring (TDM) will be pooled for the PK/PD analysis as they both provide information on PAA measurements that support the analysis. A population modeling approach will be used to describe PAA PK/PD in patients from the present study.

Individual secondary PK parameters for PAA will be derived using the population PK model:

After induction phase administration (first treatment dose):

- C_{max}: Maximum PAA after first dose (IU/L)
- T_{max}: Time of C_{max} (hours)
- $AUC_{0-\infty}$: Area under the curve of PAA-time curve from the first time of dosing (day 0), extrapolated to infinity (hrs*IU/L)
- $AUC_{0-35days}$: Area under the curve of PAA-time curve at Induction phase (day 0 to day 35 of treatment) (hrs*IU/L)

After all planned administrations:

- C_{max}: Maximum PAA (IU/L)
- T_{max}: Time of C_{max} (hours)
- $AUC_{0-91days}$: cumulative Area under the curve of PAA-time curve at induction and consolidation phase (day 0 to day 91 of treatment) (hrs*IU/L)
- $AUC_{0-203days}$: cumulative Area under the curve of PAA-time curve from induction to delayed intensification phase (day 0 to day 203 of treatment) (hrs*IU/L)

For the primary NPAA analysis, the frequency and proportion with a 2-sided 95% Clopper-Pearson CI of evaluable patients achieving NPAA ≥ 0.1 U/mL 21 days after the consolidation Day 43 dose will be summarized for the PNPAA analysis set. The primary endpoint will not be analyzed by patient group and dose level, but in a combination manner with all patients in the PNPAA analysis set.

Other PAA endpoints for patients treated at confirmed doses will also be summarized in the combined patient groups (aged 22-39 years and BMI ≤ 35 kg/m² + aged 40-54 years and BMI ≤ 35 kg/m²) who are treated at the confirmed dose levels and overall, in the PKAS. The PAA levels during induction and post-induction will be tabulated with descriptive statistics and will be plotted. The number and proportion of subjects with PAA level > 0.025, ≥ 0.1, ≥ 0.2 and ≥ 0.4 U/mL, respectively, will be tabulated by visit during induction and post-induction. The number and proportion of subjects with PAA level at any time > 0.025, ≥ 0.1, ≥ 0.2 and ≥ 0.4 U/mL will also be summarized separately for during induction and post-induction.

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5.7.2. Immunogenicity Analysis

The assessment of anti-drug antibodies includes binding antibodies to calaspargase pegol and binding anti-PEG antibodies. It will be analysed in Immunogenicity Analysis Set.

Number and proportion of patients with positive post-baseline anti-drug antibodies will be summarized. The patients with positive post-baseline anti-drug antibodies are defined as the patients with at least 1 positive reported visit during post-baseline visits. A patient with missing baseline will be considered as negative baseline to be conservative.

Immunogenicity effect on hypersensitivity and anaphylactic reaction will be explored. Among the subjects developing hypersensitivity and anaphylactic reaction, the number and proportion of subjects having positive post-baseline antibodies will be tabulated.

Immunogenicity assessments will include the detection of binding antibodies against the study drug (calaspargase pegol) as well as those antibodies that bind to PEG in samples taken during the study.

Considering the low number of subjects and the anticipated low rate of seroconversion, results will be reported as follows:

- Pre-existing anti-drug or anti-PEG antibodies: Number of samples confirmed positive at baseline versus total number of baseline samples. If the pre-dose sample at induction is missing, the baseline sample status will be considered negative.
- Seroconversion upon treatment: Number of samples converted from negative at baseline to positive after treatment.
- If a confirmed positive sample at baseline has titer increase after treatment by more than 4-fold then it will be included within the seroconverters.
- Persistence of anti-drug or anti-PEG antibodies will be evaluated based on consecutive results after treatment.

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

- On the PK through the temporal association of antibodies with the loss of asparaginase activity.
- On the safety through the potential relationships with treatment–emergent hypersensitivity and anaphylactic reactions.

6. INTERIM ANALYSIS

Not applicable.

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7. CHANGES TO PROTOCOL-PLANNED ANALYSES

Section 3.1.2

- Added one additional criterion, that patients who developed silent inactivation on or before day 21 after consolidation Day 43 dose, will be excluded from PNPAA analysis.

Section 5.7.1

- Clarified other PAA endpoints for patients treated at confirmed doses will be summarized in the combined patient groups (aged 22-39 years and BMI $\leq$ 35 kg/m^2 + aged 40-54 years and BMI $\leq$ 35 kg/m^2) who are treated at the confirmed dose levels and overall, in the PKAS rather than FAS.

Section 3.1

- No analysis will be performed in Per-protocol Analysis Set.

8. REFERENCES

9. APPENDICES

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