SPARK - ALL -

AMENDED CLINICAL STUDY PROTOCOL

Study official 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**
Study brief title	**SPARK-ALL: Calaspargase Pegol in Adults with Untreated, Ph-negative B-cell and T-cell ALL**
Study public title	**SPARK-ALL: Calaspargase pegol in Adults with 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**
Protocol code	**CL2-95015-001**
EudraCT Number	
Universal Trial Number	
Other register number (CT. gov)	**NCT04817761**
Investigational New Drug Application Number	**100594**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **22, route 128** **91190 Gif-Sur-Yvette - FRANCE**
International Coordinator	**Daniel J. DeAngelo, MD, PhD** **Dana-Farber Cancer Institute, Boston, MA**
Date of the document	**30 October 2024**
Version of the document	**Final version**
Version number	**7.0**

Substantial Amendment integrated

Version Number	Substantial Amendment Number	Final Version Date	Countries Concerned
1.0	-	11 December 2020	United States
2.0**	1	16 February 2021	United States
3.0	2	13 May 2022	United States
4.0	3	22 December 2022	United States
5.0	4	26 September 2023	United States
6.0	5	22 December 2023	United States
7.0	6	30 October 2024	United States

***Previously numbered 1.01*

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* *Note that Part 2 of this study (this version of the protocol) includes adults aged 22 to < 55 years.*

VERSION LIST

Protocol Version Number	Amendment Number	Final Version Date	Countries Concerned	Nature of Modifications
1.0	NA	11 December 2020	USA	Original protocol
2.0	1	16 February 2021	USA	- Synopsis: Estimated study initiation was changed from Q3 to Q2. - Appendix 4 and Appendix 5 were added for backbone drug information and dose modification instructions. - Table (4.1.2.1.1) 1 and Table (9.3.1) 1: An immunogenicity sample collection time point was added on Day 18 of Remission Induction; blood sample volumes were updated to reflect the additional sample. - Section 4.1.2.5: text was added to specify that blood samples will be kept until the end of FDA review of the study data. The total blood volume to be collected on study was updated to reflect the added immunogenicity sample collection. - Section 5.2.2: Enrollment criterion 14 (non-screening criteria) was revised to specify: o Known severe hepatic impairment: ▪ direct (bilirubin > 3 x upper limit of normal (ULN) (unless suspected leukemic involvement of liver). ▪ ALT/AST > 5 times ULN (unless suspected leukemic involvement of liver). - Section 8.9.1: consistent with new company policy, text was added to specify that fatal events occurring after informed consent should be reported on an AE form. - Section 5.4.1: added clarification to the exclusion criteria that patients with Ph+, Burkitt's leukemia, mixed lineage/mixed phenotype acute leukemia, and acute undifferentiated leukemia cannot participate. - Section 5.5.2.2: added clarification for male contraception requirements. - Section 6.6.3: Text was added to specify that institutional guidelines and investigator discretion may be applied to supportive care and concomitant treatment, except for prohibited treatments. - Table (6.6.3) 1: added that radiotherapy may be performed per institutional guidelines and investigator judgment. Added text to specify that erythropoietin and darbepoetin are prohibited. - Table (8.11) 1: text was added to clarify instructions for IMP-associated toxicity management for hemorrhagic and thrombotic events, for increase in AST and/or ALT and ketoacidosis management. - The End-of-cohort Meeting Template was revised to more accurately reflect Data Safety Monitoring Board (DSMB) evaluation and reporting processes.

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Protocol Version Number	Amendment Number	Final Version Date	Countries Concerned	Nature of Modifications
--	Non-substantial	21 May 2021	USA	- Clarification concerning Dexamethasone administration during Remission Induction and Delayed Intensification treatment phases. (Section 4.1.1; Section 6.4.2; Section 6.4.6). - Clarification to Table (6.6.3) 1 that strong CYP3A4 inhibitors and inducers should be used with caution but not prohibited. - Clarification is made to BMA and biopsy tissue storage requirements (Section 7.2.3). - Gamma-glutamyl transferase (GGT) analysis will be performed at End of Treatment (EOT) or Early Termination Visit. (Section 8.2.3). - The hepatotoxicity monitoring is updated for AST or ALT increase Grade 3 to be consistent with CTCAE V5.0 and Table (8.11) 1.
3.0	2	13 May 2022	USA	This amendment is considered substantial because: - Following an event of hepatotoxicity, provision is made for longer recovery periods and less stringent thresholds to be considered before withdrawing a patient. (Unacceptable toxicity definition; Hepatoxicity monitoring Section 8.6.1; Management of calaspargase pegol-associated toxicities Table (8.11) 1). - It allows the use of a pre-treatment blood sample for flow cytometry analysis in eligible patients. The total volume of blood sampled has been modified to “approximately 855 mL” (End-of-visit/Early Discontinuation visit Section 4.1.2.5). Other changes include: - It allows for a slightly greater proportion of T-cell ALL patients that previously (“approximately 75-80%”, instead of (“at least 80%”). (Synopsis & Study plan Section 4.1.1). - The PAA data required for the end-of-cohort analysis is clarified. (Synopsis & Study plan Section 4.1.1). - A new Section (6.4.7) has been added for Maintenance Therapy that clarifies the collection of safety data during this phase and before the End-of-Treatment visit. - The use of MRD results from local laboratories is included as a secondary outcome analysis. (Assessment of efficacy Section 7). - The collection of adverse events at the end of the treatment period has been clarified. (Timeframe for adverse event reporting Section 8.9.1).

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4.0	3	22 December 2022	USA	This amendment is considered substantial because: - MRD status and clinical decision-making will be determined using each site's local laboratory results. Local MRD laboratory results will be collected and analyzed as a secondary outcome. MRD assessment will also be performed centrally to support regulatory approval and the efficacy endpoint. - Removed the "investigator's discretion" caveat from eligibility criterion #20 (currently #20a) so that it now reads: Currently active second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years. Other notable changes include: - The evaluation period for UT of hypersensitivity was extended: For all UTs, except hypersensitivity, the UT assessment period is defined as within 30 days after the initial calaspargase pegol administration in the Remission Induction phase. As antibody-mediated hypersensitivity events have been reported to occur at the time of the second or third asparaginase dose, the assessment period for hypersensitivity UT only is extended from the initial calaspargase pegol administration at induction through and inclusive of the day of the third calaspargase pegol dose expected to occur on Day 43 of the consolidation phase (may occur later in the event of delayed/skipped dose). - Clarified the collection of BMA sample for cytogenetics and FISH (Table (4.1.2.1.1) 1, Table (4.1.2.2) 1, and Table (4.1.2.4) 1). - Added detail to Grade 2 CNS thrombosis in Table (8.11) 1, Management of Calaspargase pegol-associated Toxicities.
5.0	4	26 September 2023	USA	These amendments are considered substantial because: - Part 1 (dose-finding) of the study has completed, and the protocol has been amended to focus on Part 2. - Due to safety findings, the starting doses for patients ≥ 55 years of age or those with BMI >35 kg/m^2 were not confirmed in Part 1; therefore, no additional patients in these age/BMI groups will be enrolled in Part 2. - For Part 2, patients will be treated as follows: ▪ Patients aged 22 to 39 years + BMI ≤ 3 5 kg/m^2 will be treated with calaspargase pegol 1750 U/m^2 (reduced from 2000 U/m^2). ▪ Patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1500 U/m^2 (unchanged from Part 1).

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				- Added the requirement that patients who discontinue calaspargase pegol treatment early and are switched to alternate therapies will not be included in long-term follow-up. - The study sample sizes were adjusted for the reduced number of patient cohorts and reduced calaspargase pegol dose, and per historical estimates of adverse events of special interest (AESI), to provide adequate precision for safety evaluation. - Bone biopsy sampling removed from protocol. - Clarified that biomarker analysis serves to identify molecular biomarkers that may be indicative of clinical response/resistance. - Added the following EXCLUSION criteria: ▪ History of veno-occlusive disease (VOD) ▪ Patients ≥ 55 years of age ▪ Patients with BMI >35 kg/m^2 - Clarified the timing and laboratory logistics for bone marrow aspiration (BMA) and assessment of minimal residual disease (MRD, Section 7.2.3 and Section 7.2.3.2). - Added rituximab as a backbone therapy for CD20+ patients and blinatumomab at the investigator's discretion (after Consolidation, Section 6.2.1.3); also included the timing of administration of rituximab during Remission Consolidation [Table (6.4.3) 1], Interim Maintenance [Table (6.4.4) 1], and Delayed Intensification [Table (6.4.6) 1]. - Clarified that the same pre-medication regimen will be used for CD20+ patients treated with rituximab. - Clarified that calaspargase pegol will be allocated and dispensed via Randomisation and Trial Supply Management (RTSM). - Clarified that a bone biopsy is not needed unless it is a part of the site's standard practice. If a biopsy is obtained, the results should be entered onto the electronic case report form. - Added information regarding hepatic veno-occlusive disease (Section 8.12.1). - Added details regarding the collection of biomarker samples (Section 9.4). - Added drug-label details for rituximab and blinatumomab (Appendix 4). - Addition of 2 serum asparaginase activity (SAA) timepoints for plasma asparaginase activity (PAA)/SAA comparability study

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Protocol Version Number	Amendment Number	Final Version Date	Countries Concerned	Nature of Modifications
6.0	4	22 December 2023	USA	These amendments are considered substantial because: - Safety boundaries that evaluate the rate of AESIs (hyperbilirubinemia, thrombosis, pancreatitis, and hypersensitivity) are provided (Section 8.6). Once a safety boundary is reached, patient enrollment in the respective age group will be suspended until all available safety data are evaluated by the DSMB and a decision is made whether to permanently stop further enrollment. - Administration guidelines for intrathecal methotrexate (Appendix 4) duplicated in error, the administration guidelines for rituximab. The administration guidelines for intrathecal methotrexate have been corrected. - Expanded the PAA/SAA comparability text per an FDA request to provide adequate cross validation of asparaginase activities in both plasma and serum before studying the proposed dose levels in a large number of patients. Added an in vitro procedure before the start of Part 2 of the study, to support the comparability of PAA and SAA from the same blood sample. In case an in vitro experiment cannot be carried out, the sponsor will conduct a formal interim analysis of the PAA/SAA comparability after 3 to 6 patients who will provide PAA and SAA data during the study. In case the in vitro study is not deemed supportive of the cross validation of PAA and SAA, an interim analysis of the PAA/SAA comparability in 6 patients from Part 2 of the study would be performed. If this interim analysis is deemed supportive of the cross validation of PAA and SAA, the sponsor will consider to stop collecting samples for SAA in newly enrolled patients in order to reduce the burden for the patients. - Added rationale for using blinatumomab in MRD-negative as well as MRD-positive patients, along with safety monitoring and criteria for discontinuing blinatumomab-treated patients from the study. - In order to reflect the most current version of the blinatumomab USPI (June 2023): o the weight limit for 7-day infusion of blinatumomab was removed from Appendix 4. o Updated blinatumomab dose modification in Appendix 5 with the dose modification for adverse reactions from Table 3 of the current version of the USPI. - Updated study design figure and text for the administration of blinatumomab between the Interim Maintenance Phase and the Delayed Intensification Phase.

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7.0	6	30 October 2024	USA	These amendments are considered substantial because: - Throughout protocol (especially Study Design and Study Conduct): For protocol continuity, the details of completed Part 1 of the study were added back to the protocol. - Synopsis, Section 3.2 Secondary objectives, Sections 9.2.2.1 and 9.2.2.2, Section 10.1, and Schedule of Assessments (and elsewhere as applicable): Removed plasma/serum asparaginase activity comparability and sampling of SAA from the protocol, as this has been completed and is no longer a part of the protocol. - Section 6.2.1.3.1 and Appendix 4: Added immune effector cell-associated neurotoxicity syndrome as a possible significant reaction to blinatumomab (to reflect the updated blinatumomab USPI). - Section 6.2.1.3.1: Remove text: “It is recommended that the first 3 days of Cycle 1 and the first 2 days of all subsequent cycles be administered in the hospital to observe patients for cytokine release syndrome and neurotoxicity”, and added text “Please refer to blinatumomab USPI label regarding suggested number of days patients should be observed in the hospital during administration.” (Per USPI: “Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle."). - Updated Table 8.6.1 (safety boundaries) and Table 10.2.1 (sample size justification) based on pancreatitis Grade ≥3 historical estimate. - Section 6.2.1.3: Added blinatumomab was approved on June 14, 2024 in CD19-positive Philadelphia chromosome-negative B-cell precursor acute ALL in the consolidation phase of multiphase chemotherapy.” - Throughout protocol: Removed wording that dosing from Part 1 was "confirmed" and replaced with "recommended" since the 22-39 age group dosing was reduced to 1750 U/m^2 and not confirmed. - Table 4.1.2.1.1 and Section 7.2.3: Changed 1000/mL to 1000/**µL** in the text “4 mL blood sample for central testing, only in case of insufficient BMA provided there are sufficient numbers of circulating lymphoblasts (at least 1000/µL).” - For BMA/ MRD in the Screening and Remission Induction Assessment Schedule, Remission Consolidation Assessment Schedule, Delayed Intensification Assessment Schedule, and Section 7.2.3.1, the following text was added for BMA sample: “A ± 2 day window for BMA sample collection for MRD central assessment is permitted as long as the patient has adequate blood count recovery after aplasia.”

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				- Schedule of Events Tables (4.1.2.1.1) 1, (4.1.2.2) 1, (4.1.2.3) 1, (4.1.2.4) 1, End-of-Treatment assessments Table (4.1.2.5) 1, and Table (8.2) 1 (Local Clinical Laboratory Parameter Collection Plan): Added the collection of antithrombin III (ATIII) to monitor coagulopathy. - Prohibited and unauthorized treatments Table [(6.6.3) 2]: Added the prohibition of the prophylactic use of cryoprecipitate replacement for hypofibrinogenemia, unless patients have active bleeding, are at high-risk of bleeding while on full-dose anticoagulation, or are undergoing an invasive procedure. - Section 8.6.3 (Coagulopathy Monitoring): Added details of antithrombin monitoring, including the target AT nadir level.

[a] *Protocol amended prior to start of study.*
[b] *Renamed to Version 2.1.*
[c] *Version 1.01 was subsequently renumbered to Version 2.*

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SYNOPSIS

Name of the Sponsor
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Name of Finished Product
Calaspargase pegol-mknl (Asparlas, S95015)

Name of Active Ingredient
Calaspargase pegol (Asparlas, S95015)

Title of Study
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[2*] Years with Newly-diagnosed Philadelphia-negative ALL.
Protocol No.: CL2-95015-001.
Study Brief Title
SPARK-ALL: Calaspargase pegol in Adults with Untreated Ph-negative B-cell and T-cell ALL.
Study Public Title
SPARK-ALL: A Multi-center Open-label Single-arm Phase 2/3 Trial Assessing the Safety and Pharmacokinetics of Calaspargase pegol in the Treatment of Newly-diagnosed Philadelphia-negative ALL in Adults Aged 22 to > 65* Years.

Coordinator
Daniel J. DeAngelo, M.D., PhD, Dana-Farber Cancer Institute, Boston, MA.
National coordinators and investigators are listed in a separate document.

Study Centers
Up to 25 investigational centers in the United States.

Study Period
- Study duration for the participant: up to 18 months.
- Study initiation (first visit first participant): PPD.
- Estimated study completion date (Last Visit Last Patient): Q4 2026.

Study Development Phase
2/3

Objectives
The study is being conducted in 2 parts. Part 1 was a dose confirmation run-in period. Part 2 is enrolling participants at the dose(s) confirmed or recommended in Part 1. Because Part 1 of this study has been completed, the protocol has been amended to modify Part 2, based on Part 1 data. The Part 2 objectives and endpoints are described below:

Tier	Objective(s)	Endpoint(s)
Primary	Evaluate the safety of calaspargase pegol in adults	Incidence of adverse events (AEs) with focus on asparaginase class toxicities; laboratory tests (hematology, biochemistry, coagulation, liver function tests); physical examination, and vital signs
	Pharmacodynamic (PD), (nadir plasma asparaginase activity [NPAA])	NPAA $\geq$ 0.1 U/mL 21 days after the consolidation Day 43 dose (Note: NPAA is defined as the target durable day 21 time point post-administration of calaspargase pegol)
Secondary	PD (plasma asparaginase activity [PAA])	- PAA level $\geq$ 0.1 U/mL at any time during induction and post-induction, respectively - PAA level $\geq$ 0.025, $\geq$ 0.1, $\geq$ 0.2, or $\geq$ 0.4 U/mL at predefined time points during induction and post-induction, respectively
	Pharmacokinetics (PK)	PAA-derived PK parameters (*e.g.* C_{max}, AUC)
	Efficacy	- Minimal residual disease (MRD) negative status at the end of induction. - Complete remission (CR). - 1-year event-free survival (EFS), disease-free survival (DFS) and overall survival (OS). - 2-year EFS, DFS, OS. - 3-year EFS, DFS, 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.

[2*] *Note that Part 2 of this study (this version of the protocol) includes adults aged 22 to < 55 years.*

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Methodology
Calaspargase pegol will be administered along with the multi-agent chemotherapy regimen based on the CALGB 10403 study. The backbone therapies are considered non-investigational medicinal products (NIMPs).
To be consistent with the incidence of precursor B-cell acute lymphoblastic leukemia (ALL) in adults and the baseline characteristics of the population considered in the literature data, approximately 75 - 80% of the included population will be patients with B-cell ALL.
The study is being conducted in 2 parts:
Part 1 was a dose confirmation run-in period that evaluated the safety of calaspargase pegol administration and that obtained PAA data for the proposed calaspargase pegol doses in each age and body mass index (BMI) group. Part 1 of this study has been completed. A total of 26 patients had enrolled into Part 1 and were treated with calaspargase pegol as follows:

- 6 patients aged 22-39 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 2000 U/m^2.
- 4 patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 1500 U/m^2.
- 8 patients aged ≥ 55 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 1000 U/m^2.
- 8 patients aged < 55 years + BMI > 35 kg/m^2 were treated with calaspargase pegol 1000 U/m^2.

The end-of-cohort analysis in Part 1 used patient data obtained through 30 days after the Day 4 induction dose, including PAA data and the prior population PK model; the patients continued through the remaining phases of Remission Consolidation, Interim Maintenance and Delayed Intensification. The enrollment into Part 1 was completed in stages. All required data for the 2 higher dose groups (2000 U/m^2 and 1500 U/m^2) and any available safety and PAA data (through 21 days post Day 43 Remission Consolidation dose) for patients treated with the starting dose of 1000 U/m^2 were evaluated at the end of Part 1.
The safety and PAA data from Part 1 have been analyzed for the patients treated with the starting doses of 2000 U/m^2 and 1500 U/m^2. Based on this, dose adjustments for patients aged 22-39 +BMI < 35 kg/m^2 are implemented in Part 2. For Part 2, patients will be treated as follows:

- Patients aged 22 to 39 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1750 U/m^2.
- Patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1500 U/m^2 (unchanged from Part 1).

No additional enrollment of patients ≥ 55 years of age or those with BMI > 35 kg/m^2 will take place in Part 2.

Note that, patients whose BMI increases to > 35 kg/m^2 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.

As in Part 1, patients in Part 2 of the study will proceed through the treatment phases of Remission Induction, Remission Consolidation, Interim Maintenance, and Delayed Intensification. During these phases, patients will receive the dose(s) confirmed or recommended in Part 1.
The end-of-treatment visit will occur at 1 year after the initial calaspargase dose. All patients, except for those who switched to alternate therapies or withdrew consent, will participate in the long-term disease status and survival follow-up for an additional 2 years after the 1-year end-of-treatment visit. The patients will receive a telephone call once every 3 months to confirm their disease and survival status. Disease status and survival data at the clinical site will be used for long-term EFS, DFS, and survival outcome evaluation.
The study will be conducted in up to 25 sites in the United States in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and applicable regulatory requirements.

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

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Diagnosis and Main Criteria for Inclusion

Inclusion criteria:

- Male or female participants aged ≥ 22 and < 55 years with newly-diagnosed and cytologically confirmed and documented Philadelphia-negative B-cell or T-cell ALL as specified in World Health Organization (WHO) classification (*i.e.*, diagnosis of ALL requires demonstration of ≥ 20% bone marrow lymphoblasts upon hematopathology review of bone marrow aspirate and biopsy materials).
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2.
- No prior therapy for ALL such as chemotherapy and radiation therapy before signing the informed consent except for limited treatment (≤ 7 days) with corticosteroids or hydroxyurea and a single dose of intrathecal cytarabine.

Exclusion criteria:

- Patients with Philadelphia chromosome positive ALL, Burkitt's leukemia, mixed lineage/mixed phenotype acute leukemia, and acute undifferentiated leukemia per WHO classification (2016).
- Patients with Down syndrome.
- Patients with Hepatitis B (positive for HBs antigen), and Hepatitis C (HCV antibody) at inclusion
- Participants known to be human immunodeficiency virus (HIV)-positive.
- Known history of non-gallstone-related pancreatitis.
- Known severe hepatic impairment (bilirubin ≥ 3 x upper limit of normal [ULN]; ALT/AST > 5 times ULN)
- Pre-existing history of hepatic veno-occlusive disease (VOD).
- Age ≥ 55 years.
- BMI > 35 kg/m^2.

Investigational Medicinal Product

Calaspargase pegol as provided, contains 5 mL of extractable volume of concentration 750 U/mL in a single-dose vial. Calaspargase pegol will be administered via a 2-hour intravenous infusion at a dose level based on age and BMI (see dose levels in table below). 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.

The age/BMI and dose groups in Part 2 of the study are as follows:

Calaspargase pegol Doses for Part 2

Population	Calaspargase pegol doses
Adults aged 22 to 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

BMI = body mass index

Premedication

Patients will receive premedication (see Section 6.1.1) prior to calaspargase pegol administration: acetaminophen, histamine-1 blocker, and corticosteroids to prevent a hypersensitivity reaction.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) for PAA will be performed at Days 7, 14, and 21 after each calaspargase pegol dose at each treatment phase to ensure adequate dosing. The results will be available to Investigators in real time.

Backbone Therapy

Patients will receive other backbone chemotherapy agents based on the CALGB 10403 protocol treatment regimen.

Comparator
Not applicable

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Duration of Treatment

- **Screening Period**: up to 21 days.
- **Active Study Drug Treatment Period** (includes: Remission Induction, Remission Consolidation, Interim Maintenance, and Delayed Intensification): ~9-12months.
- **Long-term Follow-up Period**: a total of 3 years after the initial calaspargase pegol administration (i.e., up to a total of 3 years after completion of the Active Study Treatment Period).
- **Maintenance Period**: this treatment cycle is administered per study CALGB 10403 treatment regimen at physician discretion, and is not part of the active treatment protocol. Total duration of maintenance therapy is 2 years from the start of Interim Maintenance for female patients and 3 years from the start of Interim Maintenance for male patients.

Patients will be evaluated for eligibility during the screening period of ≤ 21 days prior to treatment initiation. The initial dose of calaspargase pegol will occur at Day 4 (or 5, or 6) in the Remission Induction phase. Treatment with calaspargase pegol will continue through the Remission Consolidation and Interim Maintenance phases, with the last dose of calaspargase pegol administered on Day 43 in the Delayed Intensification phase. The end-of-treatment visit will occur 1 year after the initial calaspargase pegol administration. Subsequently, a telephone call to the patient every 3 months will occur for an additional 2 years for long-term disease and survival status follow-up.

Criteria for Evaluation:
Efficacy Measurements

Complete Remission

Complete remission will include morphologic complete remission rate (CR) and morphologic complete remission rate with incomplete blood count recovery (CRi).

Minimal Residual Disease (MRD)

MRD status and clinical decision-making will be determined using each site's local laboratory results; these results will be collected in the clinical database. MRD assessment will also be performed centrally to support regulatory approval and the secondary efficacy endpoint.

For central MRD assessment, 2 mL of first aspirate BMA will be collected at each specified time point. Local assessment of MRD will be performed according to institutional practices.

The tumor load will be evaluated all along the study up to the end-of-treatment visit:

- Pre-treatment.
- During Remission Induction phase at Day 29 (± 2 days).
- During Remission Consolidation phase at Day 56 (± 2 days).
- During Delayed Intensification phase at Day 50 (± 2 days).
- In case of premature withdrawal (at the Investigator's discretion).
- At any time in case of suspicion of disease relapse up to the Investigator's judgement.
- At the End-of-Treatment visit (at the investigator's discretion)

Note that a bone biopsy is not needed unless it's a part of a site's standard practice. If a biopsy is obtained, the results should be entered onto the electronic case report form.

Patients with M3 or M4 marrow (greater than 25% lymphoblasts) at the end of Remission Induction therapy will not be eligible for the Remission Consolidation phase and will be discontinued. If at the end of the Remission Consolidation phase there is evidence of MRD, as demonstrated by MRD > 10^{-4} detectable leukemia cells in the bone marrow, any further treatment will be based on Investigator discretion. If hematopoietic stem cell transplantation or any other non-protocol treatments are indicated, the patient will be discontinued from the study treatment.

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Other Efficacy Endpoints

- EFS will be defined as the time from first calaspargase pegol treatment to the date of the documented relapse, including induction failure, diagnosis of a second malignant neoplasm, or death from any cause, whichever comes first.
- DFS will be defined as the time from achievement of complete remission to the documented relapse, diagnosis of a second malignant neoplasm, or death from any cause, whichever comes first, for subjects who achieve a CR.
- Overall survival (OS) will be defined as the time from first calaspargase pegol treatment to death from any cause.

Safety Measurements

AEs/treatment-emergent adverse events (TEAEs), including adverse events of special interest (AESI), laboratory AEs; physical examination, vital signs including height, weight, body surface area (BSA), BMI will be collected. Safety assessments will be performed throughout the study and reported at each visit during the treatment period. The safety assessments will include:

- AEs.
- Physical examinations and performance status.
- Vital signs.
- Laboratory assessments, including hematology, blood biochemistry, urinalysis, coagulation parameters and hepatitis serology.
- Electrocardiogram (ECG) assessments.
- Echocardiography or multiple-gated acquisition (MUGA) scan.
- Pregnancy tests for women of childbearing potential.
- Recording of any change or addition of a new concomitant treatment.

Adverse events will be collected regardless of seriousness or study drug relationship and will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria Version 5.0.

Toxicities will be managed as described in Table (8.11) 1. For the backbone therapies, the management of the toxicities will be done according to the corresponding United States Prescribing Information (USPI).

Safety boundaries that evaluate the rate of AESIs (hyperbilirubinemia, thrombosis, pancreatitis, and hypersensitivity) are included in the protocol. Once a safety boundary is reached, patient enrollment will be suspended until all available safety data are evaluated by the DSMB and a decision is made whether to permanently stop further enrollment. Additionally, once a safety boundary is reached, patients who have not yet been administered the study drug will have the dose withheld.

Pharmacokinetic Measurements/Plasma Asparaginase Activity

Pharmacokinetic analysis and TDM will be performed at a centralized laboratory (BioAgilytix).
Blood samples for PAA evaluation will be collected at:

- Induction: Pre-dose and 24 hours and 48 hours post dose.
- Post-Induction: Pre-dose and 24 hours post-dose (exact time points are defined in Section 9.2.1).
- TDM will be done pre-dose and at Days 7, 14, and 21 post-dose to monitor for adequate asparagine depletion demonstrated by PAA ≥ 0.1 U/mL. The results will be available to Investigators in real-time (the process and methodology are defined in Section 9.2.2).

Immunogenicity

Anti-calaspargase pegol and anti-polyethylene glycol (PEG) antibodies will be assessed pre-dose and during the different phases of the study treatment (Remission Induction, Remission Consolidation, Interim Maintenance, and Delayed Intensification), at Day 18 and 29 in the Remission Induction, and at at the end of treatment or at treatment and study discontinuation. This evaluation will be based on qualitative enzyme-linked immunosorbent assay (ELISA) using calaspargase pegol as coating antigen. The assays follow a multi-tiered approach consisting of a screening assay, a confirmatory assay, a titer assay, and a specificity assay. All positive samples will be further confirmed by competitive ELISA for the presence of binding antibodies against calaspargase pegol. Samples, when confirmed positive, will then be assayed for the antibodies against PEG.

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Name of Active Ingredient
Calaspargase pegol (Asparlas, S95015)

Exploratory Biomarkers
The purpose of the exploratory biomarker assessments of pre-treatment samples is to explore expression/mutation of genes or translocations that might be of predictive or prognostic significance. Comparison of pre- and post-treatment samples might help understand the mechanism of resistance of the study drug.

Statistical Analysis
Analysis Data Sets
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 safety analyses, including AEs, exposure to study treatment, concomitant medications and other safety data. Secondary efficacy analyses will also be conducted using the FAS.

Primary NPAA Analysis Sets
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 $\leq$ 35 kg/m^2+aged 40-54 years and BMI $\leq$ 35 kg/m^2) who are treated at the recommended dose levels.
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 or had any other factors that may impact the interpretability of the PNPAA analysis.

Per-protocol Analysis Set
The per-protocol analysis set (PPAS) will include all subjects in the FAS population who did not have any major protocol violations. All decisions to exclude subjects from the PPAS will be made prior to the database lock for the final analysis and the rules will be included in a separate document.

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.

Immunogenicity Analysis Set
The immunogenicity analysis set 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.

Analyses
Unless otherwise specified, all analyses will be conducted by patient group and dose level if estimable. Dose level designation for each patient is determined based on the first dose that patient received.

Primary Analysis
AEs, Key AEs, and Laboratory Evaluations: Descriptive summary statistics including the number and percentage of patients having each treatment-emergent adverse event (TEAE) in the FAS will be provided by patient group and dose. All TEAE including deaths will be listed. Key AEs will be analyzed separately using the FAS. The frequency and proportion with a 2-sided 80% Clopper-Pearson confidence interval (CI) of each key AE will be summarized.
Primary NPAA Analysis: The frequency and proportion with a 2-sided 95% Clopper-Pearson CI of evaluable patients achieving NPAA $\geq$ 0.1 U/mL 21 days after the consolidation Day 43 dose will be summarized for the PNPAA analysis set.

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Secondary Analyses

PK: A population modeling approach will be used to describe the PK/PAA in adult patients in this study. Individual PK parameters such as area under the plasma asparaginase activity-time curve (AUC) or maximum observed plasma asparaginase activity (C_{max}) will be derived using the population PK model. The population modeling analysis will be described in a separate data analysis plan (DAP). Exploratory assessment of the relationship between individual PK parameters and PD endpoints for efficacy or safety might be performed and, if applicable, a separate data analysis plan (DAP) will be written.

MRD: The frequency and proportion of patients achieving end-induction MRD-negative status will be summarized along with the 95% Clopper-Pearson CIs.

CR: The frequency and proportion of patients achieving complete remission will be summarized along with the 95% Clopper-Pearson CIs.

PAA: PAA levels during induction and post induction will be tabulated with descriptive statistics and plotted. The frequency and proportion with a 2-sided 95% Clopper-Pearson CI of patients achieving PAA ≥ 0.1 U/mL at any time during induction and post-induction, respectively, will be summarized. The number and proportion of patients with PAA level ≥ 0.025, ≥ 0.1, ≥ 0.2, or ≥ 0.4 U/mL will be tabulated by visit.

Individual PK/PAA parameters will be derived from the population PK analysis for each patient of the PKAS and tabulated with descriptive statistics.

Survival: DFS, EFS, and OS rates at 1 year, 2 years, and 3 years will be provided along with the 95% CIs estimated using the Kaplan-Meier method.

Immunogenicity: The number and proportion of patients having anti-calaspargase pegol ± anti-PEG antibodies before and after the administration of calaspargase pegol will be summarized respectively.

Exploratory Analyses

The frequency and proportion of end-consolidation MRD-positive subjects with post consolidation MRD-negative status will be summarized.

Sample Size Justification

The study consisted of 2 parts for each of the patient groups. Part 1 was a dose confirmation run-in period; patients in the current Part 2 of the study will be treated at the corresponding recommended doses. The number of patients treated at recommended doses (Part 1 and Part 2 combined) and in the Part 2 patient groups (22 to 39 years of age + BMI ≤ 35 kg/m² and 40 to < 55 years of age + 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 assumption for the true proportion of evaluable patients achieving the target NPAA level for the combined Part 2 patient groups treated at the recommended dose levels, and a corresponding threshold of 85% for the 95% CI lower bound, a minimum of 56 evaluable higher dose patients treated at the recommended doses are required to provide at least 90% power.

Per historical estimates of AESIs, a total of 60 patients will be sufficient to provide adequate precision for safety evaluation. The study will stop enrollment when 56 patients are evaluable for NPAA and a minimum of 60 patients are evaluable for safety.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) has been convened to review the patients' safety data periodically throughout the study in order to ensure that the patients' potential benefit is not compromised by safety concerns in accordance with the DSMB charter. The DSMB consists of an independent group of experts who provide their expertise and recommendations to the Sponsor. Their primary responsibility is to review safety data in the light of the benefit-risk ratio on a regular basis. After each meeting they provide written recommendations regarding the progress and conduct of the study (continuation, modification, or termination).

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, and the applicable regulatory requirements. ***COORDINATOR / INVESTIGATOR:***	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
DIRECTOR OF ONCOLOGY THERAPEUTIC AREA – LATE STAGE & LCM	
NAME	PPD
DATE	
SIGNATURE	PPD

Other Sponsor's Signatories	
BIOSTATISTICS HEAD:	
NAME	PPD
DATE	
SIGNATURE	PPD

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Abbreviations/Glossary

6-MP	6-mercaptopurine
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATT	antithrombin III
AUC	area under the plasma asparaginase activity-time curve
AYA	adolescent and young adult
BID	twice daily
BMA	bone marrow aspiration
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
C_{max}	maximum observed plasma asparaginase activity
CNS	central nervous system
CR	complete remission
CrCL	creatinine clearance
Cri	incomplete blood count recovery
CRO	contract research organization
CSF	cerebrospinal fluid
Css	steady-state serum concentration
CT	computerized tomography
CTV	clinical target volume
CV	curriculum vitae
CYP	cytochrome P450
D5W	Dextrose 5% in water
DAP	data analysis plan
DEHP	di-ethylhexylphthalate
DFS	disease-free survival
DI	Delayed Intensification
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic case report form
EEA	European Economic Area
EFS	event-free survival

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ELISA	enzyme-linked immunosorbent assay
EOT	End-of-Treatment
EVA	ethyl vinyl acetate
FISH	fluorescence in situ hybridization
FAS	full analysis set
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor (filgrastim)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor (sargramostim)
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
HSCT	hematopoietic stem cell transplantation
HVL	half-value layer
hyper-CVAD	cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cycles of high-dose methotrexate and cytarabine
IM	intramuscular
IRB	Institutional Review Board
I.R.I.S.	Institut de Recherches Internationales Servier
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICRU	International Commission on Radiation Units and Measurements
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IT	intrathecal
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LTFU	Long-term follow-up
MA	marketing authorization
MAH	marketing authorization holder

MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MP	monitoring plan
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTX	methotrexate
MUGA	multiple-gated acquisition
NaCl	sodium chloride
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF	National Formulary
NGS	next generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal product
NPAA	nadir plasma asparaginase activity
NR	no response
NS	normal saline
OS	overall survival
PAA	plasma asparaginase activity
PAS	primary nadir plasma asparaginase activity analysis set
PD	pharmacodynamic(s)
PDI	planned dose intensity
PEG	polyethylene glycol
PET	positron emission tomography
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PML	progressive multifocal leukoencephalopathy
PNPAA	primary nadir plasma asparaginase activity
PO	orally
PPAS	per-protocol analysis set
Protocol treatment	chemotherapeutic regimen used in the study, including the backbone agents and calaspargase pegol
PPS	Per Protocol Set
PT	prothrombin time
PT-INR	prothrombin time and international normalized ratio
PTT	partial thromboplastin time
PTV	planning target volume
PVC	polyvinyl chloride
QS	quantum satis
RBC	red blood cells
RDI	relative dose intensity
RTSM	Randomization and Trial Supply Management
SAA	serum asparaginase activity
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous

SC-PEG	succinimidyl carbamate polyethylene glycol
SD	standard deviation
SPD	greatest perpendicular diameters
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
UT	unacceptable toxicity
Vd	volume of distribution
VOD	veno-occlusive disease
WBC	white blood cells
WHO	World Health Organization
WMA	World Medical Association

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1 ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-sponsor parties, Sponsor parties, and contract research organizations responsible for local management of the study are described in a separate document entitled: "Administrative part of clinical study protocol."

The composition and role of the supervisory committees are described in Sections 8.10 and 12.4.

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2 BACKGROUND INFORMATION

2.1 Overview of Disease Epidemiology

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid neoplasms that result from monoclonal proliferation and accumulation of lymphoblasts in the bone marrow, peripheral blood, and other organs. It is the most commonly diagnosed cancer in children but is less common in adults. Still, ALL is a very rare disease with an age-adjusted incidence rate of 1.7 per 100,000 in the United States (US) (Howlader et al, 2017). Remarkable progress have been made in the treatment of childhood ALL (Cecconello et al, 2019; Pulte et al, 2009; Rowe et al, 2005; Stock (a) et al, 2011).

Adults have less encouraging historical 5-year survival rates that have not improved significantly over the past 30 years. Adults in the United States with ALL tend to go untreated or are treated with hyper-CVAD regimens (cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cycles of high-dose methotrexate and cytarabine) with only a select group of academic institutions using asparaginase in adults as part of multi-agent ALL treatment.

Considering the inadequate outcome of ALL adult regimens, there is a critical unmet need for improving therapeutic approaches.

2.2 Asparaginase in Acute Lymphoblastic Leukemia

In pediatric population, the treatment of ALL includes long-term use of multiagent chemotherapy, of which asparaginase is a cornerstone component.

Asparagine is a nonessential amino acid for normal cell growth but is considered essential for leukemic cells as these cells are dependent on exogenous sources of asparagine for survival. Asparaginase selectively kills leukemic cells by depleting asparagine levels (Asselin et al, 1999). Native *Escherichia coli*-derived 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 et al, 2010) and/or the neutralization of asparaginase activity without any signs of hypersensitivity (*i.e.*, silent inactivation) (Tong et al, 2014). Moreover, *E. coli* L-asparaginase has to be administered frequently (*i.e.*, 3-times weekly), as the drug has a very short elimination half-life (Asselin et al, 1999).

Consequent to these limitations, pegylated formulations of *E. coli* L-asparaginase have been developed, including Oncaspar (pegaspargase), with an initial approval in 1994, and Asparlas (calaspargase pegol-mknl), approved in December 2018.

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Asparaginase is a critical component of multi-agent chemotherapy for ALL (Malard et al, 2020). Clinical studies have demonstrated that survival rates for patients with ALL are 34-53% higher when asparaginase is added to the standard ALL backbone treatment regimen (Siegel et al, 2018). As such, while initially employed predominantly in children, asparaginase is being used increasingly more frequently in the adult population. Numerous clinical trials have been conducted to date with a special focus on its safety in adults (Daley et al 2019; Derman et al, 2020; Hanbali et al, 2019; Silva et al, 2019; Stock (b) et al, 2019). It has been repeatedly demonstrated that treating adolescents and young adults (AYAs) up to age 39 years with ALL, particularly if using a pediatric-inspired regimen, improves event-free survival (EFS) and overall survival (OS) compared with adult regimens, with safety outcomes comparable to those in pediatric trials. Clinical trials in adults aged > 40 years have shown that pediatric-like regimens improve outcomes in this age group as well, with tolerable toxicity that can be managed. It has been reported that repeated PEGylated asparaginase dosing is safe in adults aged 18-60 years even after occurrence of a drug-related toxicity.

Calaspargase pegol is a PEGylated conjugate of L-asparaginase and is similar to Oncaspar. Like Oncaspar, calaspargase pegol is composed of L-asparaginase PEGylated with an approximately 5000 Da polyethylene glycol (PEG) moiety. However, calaspargase pegol uses a shorter and more chemically stable succinimidyl carbamate PEG (SC-PEG) linker to increase the plasma half-life by approximately 3-fold and permit less frequent (every 21 days) dosing. L-asparaginase catalyzes the conversion of L-asparagine into aspartic acid and ammonia.

2.3 Rationale for the Study

Calaspargase pegol-mknl (also referred to as Servier code S95015 or Asparlas) was approved in the United States in 2018 for the treatment of ALL in pediatric and young adult patients from one month of age to 21 years.

Pediatric-inspired regimens, with their more intensive use of the non-myelosuppressive drugs including corticosteroids, L-asparaginase and vincristine, and longer and more intensive central nervous system (CNS)-directed therapy and longer duration of maintenance therapy have demonstrated substantial improvements in OS.

Recent adaptations of pediatric regimens to the adult population, with pegaspargase (Oncaspar) as a critical component, have shown promise in the improvement of outcomes. In Study CALGB 10403, which enrolled adult patients up to age 40 years with newly diagnosed ALL, the median EFS was 78.1 months (95% confidence interval [CI], 41.8 to not reached) with a 3-year EFS was 59% (95% CI, 54%-65%) and the median OS was not reached. The most frequently reported toxicities were hyperbilirubinemia, pancreatitis and thrombosis (Stock (b) et al, 2019).

To date, the C10403 cooperative group trial is the largest prospective trial to evaluate the use of a pediatric regimen with pegaspargase in young adults. Feasibility of the single arm design developed in a Children's Oncology Group protocol for high-risk children and all adolescents with ALL was considered successful, with full accrual completed as planned; the adult study accrued 317 patients (Stock (c) et al, 2014). The CALGB 10403 treatment protocol is now a standard of care in the treatment of adolescents and young adults and adults with ALL.

With regard to Asparlas, the nonclinical studies confirmed its ability to deplete circulating levels of L-asparagine. The intravenous (IV) pharmacokinetic (PK) profiles of Asparlas and Oncaspar were comparable in rats and dogs and the toxicity profiles were considered similar.

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The Asparlas clinical development program and clinical pharmacology analyses demonstrated that Asparlas 2500 U/m^2 administered every 3 weeks provides comparable asparaginase activity to that of Oncaspar 2500 U/m^2 administered every 2 weeks. In the pediatric population (in Studies DFCI 11-001 and AALL07P4), Asparlas 2500 U/m^2 and Oncaspar 2500 U/m^2 yielded comparable efficacy outcomes in terms of minimal residual disease (MRD), complete remission (CR), and survival outcomes of EFS, disease-free survival (DFS) and 4-year OS.

The key risks observed in these clinical studies were in line with those previously described with the asparaginase class. The most common adverse reactions with Oncaspar (reported with a frequency of > 10% and considered related to the use of the drug) included: alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, hypofibrinogenemia, activated partial thromboplastin time (aPTT) prolonged, hypertriglyceridemia, hyperglycemia and febrile neutropenia.

The most severe adverse reactions with Oncaspar (graded 3 or 4) consistently reported in all studies with a frequency of > 5% include: anaphylactic reaction, ALT increased, AST increased, blood bilirubin increased, hypoalbuminemia, febrile neutropenia, blood fibrinogen decreased, hyperglycemia, lipase increased, pancreatitis, hypoglycemia, embolism, aPTT prolonged, and hypersensitivity. As Studies AALL07P4 and DFCI 11-001 were conducted using Oncaspar as a comparator arm, it was possible to validate the consistency of the Asparlas safety profile with the Oncaspar safety profile and to confirm that there were no unexpected risks based on the types of adverse events (AEs) observed in the pediatric population.

CL2-95015-001 is an 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 in 2 parts: Part 1 was a dose confirmation run-in period that evaluated the safety of calaspargase pegol administration and that obtained plasma asparaginase activity (PAA) data for the proposed calaspargase pegol doses in each age and body mass index (BMI) group.

Part 1 has completed. For protocol continuity, Part 1 objectives/endpoints and methods and procedures are included in this version of the protocol. However, **only Part 2 study procedures and methods are to be followed during study conduct**.

2.4 Dose Selection Rationale by Patient Group

2.4.1 Adults Aged 22 to 39 Years with BMI ≤ 35 kg/m²

2.4.1.1 Part 1

In the completed Part 1 of this study, adults aged 22 to 39 years (and having a BMI ≤ 35 kg/m²) received calaspargase pegol 2000 U/m^2 at specified time points. This dose was consistent with the dose in the Oncaspar label recommended for patients with ALL over the age of 21 years, and was further supported by Oncaspar PK in adults with newly diagnosed ALL. After a single 2000 U/m^2 IV dose during induction, the population average asparaginase activity correlated well with serum asparagine deamination. Furthermore, asparaginase activity following PEG-asparaginase administration was long lasting, with 81% of patients showing complete deamination of asparagine (as demonstrated by serum asparaginase activity (SAA) > 0.1 U/mL) at 21 days post administration.

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This dose was further supported by Monte Carlo simulations performed by Servier for adults 22 to 50 years based on the previously available calaspargase pegol population model built on PK/SAA data from 2 large, randomized trials with calaspargase pegol (AALL07P4 and DFCI 11-001). According to the simulations based on the proposed dosing strategy, the dose of 2000 U/m^2 allows ≥ 99% of adult patients to achieve the therapeutic SAA threshold post induction and remain above the level of 0.1 U/mL up to 21 days after each administration.

2.4.1.2 Part 2

Based on data from 6 patients in Part 1, the calaspargase pegol dose of 2000 U/m² showed an acceptable safety profile with adequate PAA levels. Lower doses that would still result in adequate PAA levels were explored through simulations using the available population PK model. The dose of 1750 U/m² was selected for this age/BMI group, based on the simulations. These simulations demonstrated that, based on the proposed dosing strategy, the dose of 1750 U/m² allow ≥ 95% of adult patients to achieve the therapeutic PAA threshold and remain above the level of 0.1 U/mL up to 21 days after each administration.

2.4.2 Patients Aged 40 to < 55 years with BMI ≤ 35 kg/m²

2.4.2.1 Part 1

In the completed Part 1 of this study, patients aged 40 to < 55 years (and having a BMI ≤ 35 kg/m²) received 1500 U/m^2 calaspargase pegol IV. In a study by Vyas *et al*, therapeutic SAA trough levels were observed among all induction samples with PEGylated asparaginase formulation using 1500 U/m^2, and these were sustained for 14 days after each dose (Vyas et al, 2018). Simulations based on the previous calaspargase pegol population PK model for this dose demonstrated that ≥ 97% of adult patients post induction would achieve the therapeutic SAA threshold and remain above 0.1 U/mL up to 21 days after each administration.

2.4.2.2 Part 2

Based on data from 4 patients in Part 1, the calaspargase pegol dose of 1500 U/m² showed an acceptable safety profile with adequate PAA levels. PK simulations demonstrated that, based on the proposed dosing strategy, the dose of 1500 U/m² allow ≥ 92% of adult patients to achieve the therapeutic PAA threshold and remain above the level of 0.1 U/mL up to 21 days after each administration. Therefore, this dose will continue to be administered to patients in this age/BMI group.

2.4.3 Patients Aged ≥ 55 Years with BMI ≤ 35 kg/m²

2.4.3.1 Part 1

In the completed Part 1 of this study, patients of advanced age, ≥ 55 years with BMI ≤ 35 kg/m², who were at increased risk for clinically significant treatment toxicities, were treated with calaspargase pegol at 1000 U/m^2. Derman *et al.* reported that 100% of adult patients (median age: 49.0 [19 to 76] years) who received 1000 U/m^2 of Oncaspar achieved SAA level > 0.1 U/mL at least 7 days post administration (Derman et al, 2020). These patients demonstrated fewer Grade 3-4 toxicities compared to the full dose, with preserved therapeutic effect. Simulations based on the calaspargase pegol population PK model for this dose demonstrated that ≥ 86% of adult patients would achieve the therapeutic SAA threshold from the second dose post-induction and would remain above 0.1 U/mL up to 21 days after each subsequent administration.

2.4.3.2 Part 2

Due to the occurrence of unacceptable toxicities and low PAA levels in patients ≥ 55 years, this age/BMI group has been discontinued, and patients ≥ 55 years of age will no longer be enrolled into this study.

2.4.4 Patients Aged < 55 Years with BMI > 35 kg/m²

2.4.4.1 Part 1

In the completed Part 1 of this study, patients with high BMI (> 35 kg/m^2), with an increased risk for clinically significant hepatic toxicities, were treated with calaspargase pegol at 1000 U/m^2. A Scientific Advisory Board consisting of experts in the treatment of adults with ALL was convened to discuss the suitability of the 1000 U/m^2 calaspargase pegol dose in this population. The consensus opinion at the time of Part 1 initiation was that a lower dose of 1000 U/m^2 calaspargase pegol dose was appropriate for adults with high BMI. During the conduct of Part 1 of this study, a patient experienced an event of intraparenchymal hemorrhage and sinus venous thrombosis in the cohort with adults age < 55 years and BMI > 35 kg/m^2; these events were considered unacceptable toxicities that were considered related to calaspargase pegol and, based on Data Safety Monitoring Board (DSMB) recommendation, the sponsor decided to discontinue this age/BMI group.

2.4.4.2 Part 2

Patients with BMI > 35 kg/m² will not be enrolled into this part of the study.

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3 STUDY OBJECTIVES AND ENDPOINTS

The Part 1 (completed) and Part 2 (ongoing) objectives and endpoints are described below and summarized in Table (3.4) 1 and Table (3.4) 2, respectively.

Note that although Part 1 objectives, endpoints, and methods are provided in this protocol, the conduct of this study is for Part 2 of this study.

3.1 Primary Objectives

3.1.1 Part 1 (Completed)

The primary objective of Part 1 of this study was to confirm the recommended doses for Part 2 using safety and plasma asparaginase activity data (PAA) in the 4 different age groups:

- Young adults aged 22 to 39 years and 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 (**Note: patients ≥ 55 years of age will not be enrolled into Part 2**)
- Adults aged < 55 years and BMI > 35 kg/m^2 (**Note: patients with BMI > 35 kg/m^2 will not be enrolled into Part 2**)

3.1.2 Part 2 (Ongoing)

The primary objectives of Part 2 of this study are as follows:

- 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 (AESI).

3.2 Secondary Objectives

3.2.1 Part 1 (Completed)

- 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).

3.2.2 Part 2 (Ongoing)

- 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).

3.3 Exploratory Objectives (Parts 1 and 2)

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

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3.4 Endpoints

The study endpoints for Part 1 (completed) and Part 2 (ongoing) are listed in Table (3.4) 1 and Table (3.4) 2, respectively. Details on the assessment of efficacy, safety, and other assessments are provided in Section 7, Section 8, and Section 9, respectively.

Table (3.4) 1 - Part 1 (Completed) 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 (4.1.3.3) - 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; 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 (3.4) 2 - Part 2 (Ongoing) 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 postinduction, 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.

4 STUDY DESIGN

4.1 Investigational Plan

4.1.1 Study Plan

CL2-95015-001 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, originally including adults aged > 65 years. Based on findings during Part 1 of this study, the protocol now includes only patients ≥ 22 to < 55 years of age. Patients with cytologically-confirmed Philadelphia-negative B-cell or T-cell ALL as specified in World Health Organization (WHO) classification (Arber et al, 2016; Vardiman et al, 2009), will be included in the study. The study is being conducted to assess calaspargase pegol safety, tolerability, PK, PD, and anti-leukemic activity in adults. Calaspargase pegol will be administered along with the multi-agent chemotherapy regimen based on the CALGB 10403 study (see Figure (4.1.1) 1). The backbone therapies (described in Section 6.6.2), and other treatments given at the investigator's discretion) are considered non-investigational medicinal products (NIMPs).

To be consistent with the incidence of precursor B-cell ALL in adults and the baseline characteristics of the population considered in the literature data (Terwilliger et al, 2017), approximately 75 to 80% of the included population will be patients with B-cell ALL.

The study is being conducted in 2 parts (Figure (4.1.1) 1). Part 1, which has been completed, was intended to be 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 age group. The calaspargase pegol dose was based on the patients' age and BMI.

Approximately 4 to 8 patients were to be enrolled per each of the 4 patient groups; the Part 1 dose groups and final enrollment in each group are summarized in Table (4.1.3) 1. The end-of-cohort analysis in Part 1 used patient data obtained through 30 days after Day 4 induction dose including PAA data and the prior population PK model; the patients continued through the remaining phases of Remission Consolidation, Interim Maintenance, and Delayed Intensification through the end-of-study visit.

The data for all patients in the 2 higher dose groups planned to be enrolled in Part 1 and all available data for as many patients ≥ 55 years of age with BMI ≤ 35 kg/m^2 or BMI > 35 kg/m^2 who were able to be enrolled in Part 1 were evaluated. Enrollment into Part 2 commenced upon dose confirmation (or dose adjustment if required) following review of all safety and PAA data obtained during the PAA observation period in Part 1 (21 days after second consolidation dose).

While the sample size for Part 1 was based on the simulation data from the pediatric population PK model, the sample size for Part 2 was adjusted taking into consideration the observed PAA data in adults, along with the clinical assumptions based on the observed PAA data in the pediatric studies with calaspargase pegol.

The study (Part 2) will stop enrollment when at least 56 patients are evaluable for NPAA and a minimum of 60 patients are evaluable for safety. At the end of the Part 1, 2 subjects were evaluable for NPAA to be included in the Primary Nadir Plasma Asparaginase Activity Analysis Set (described in Section 10.1.1.2).

Per the protocol, Part 2 of this study commenced after the required safety and PAA data were analyzed for the patients treated with the starting doses of 2000 U/m^2 and 1500 U/m^2. These analyses have occurred, and based on these analyses, the needed dose adjustments, study design modifications, and the number of patients to be treated in Part 2 have been made.

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For Part 2, patients will be treated as follows:

- Patients aged 22 to 39 years + BMI ≤ 35 kg/m^2 will be treated with 1750 U/m^2 (dose reduced from 2000 U/m^2 in Part 1).
- Patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1500 U/m^2 (unchanged from Part 1).

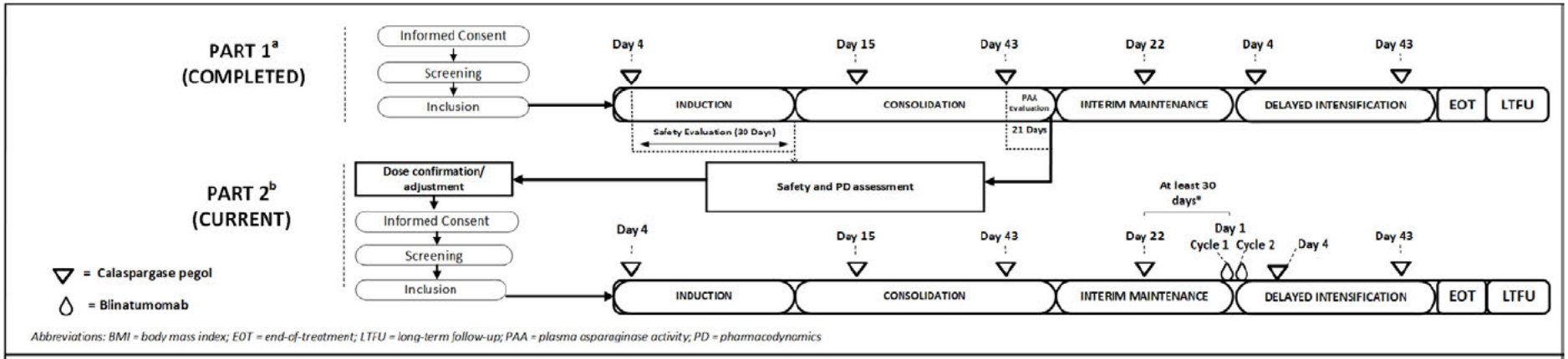
Note that, based on the safety and PAA data obtained in Part 1, no additional enrollment of patients ≥ 55 years or patients with BMI > 35 kg/m^2 will take place in Part 2.

Patients whose BMI increases to > 35 kg/m^2 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.

The study will be conducted in at up to 25 sites in the United States in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1) and applicable regulatory requirements.

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Figure (4.1.1) 1 - CL2-95015-001 Study Plan



Abbreviations: BMI = body mass index; EOT = end-of-treatment; LTFU = long-term follow-up; PAA = plasma asparaginase activity; PD = pharmacodynamics

THERAPEUTIC REGIMEN

Remission Induction Therapy	Remission Consolidation Therapy	Interim Maintenance Therapy	Between Interim Maintenance and Delayed Intensification Therapy	Delayed Intensification Therapy
Day 1: Cytarabine 70 mg intrathecal **Days 1-7; 15-21: Dexamethasone** 5 mg/m^2 PO or IV BID **Days 1, 8, 15, 22: Vincristine** 1.5 mg/m^2 IV (maximum dose 2 mg) **Days 1, 8, 15, 22: Daunorubicin** 25 mg/m^2 IV **Day 4: Calaspargase pegol** 1500 and 1750 U/m^2 IV (Part 2)[b] **Days 8, 29: Methotrexate** 15 mg intrathecal (also administered on Days 15, 22 for patients with CNS3)	**Days 1, 29: Cyclophosphamide** 1000 mg/m^2 IV **Days 1-4, 8-11, 29-32, 36-39: Cytarabine** 75 mg/m^2 IV or SC **Days 1-14, 29-42: 6-Mercaptopurine** 60 mg/m^2 orally **Days 15, 22, 43, 50: Vincristine** 1.5 mg/m^2 (maximum 2 mg) IV **Days 15, 43: Calaspargase pegol** 1500 and 1750 U/m^2 IV (Part 2)[b] **Days 1, 8, 15, 22: Methotrexate** 15 mg intrathecal (omit doses on Days 15 and 22 for patients with CNS3) **Days 1, 8, 29, 36: Rituximab** 375 mg/m^2 IV	**Days 1, 11, 21, 31, 41: Methotrexate** at a starting dose of 100 mg/m^2 IV escalated by 50 mg/m^2/dose **Days 1, 11, 21, 31, 41: Vincristine** 1.5 mg/m^2 IV (maximum dose 2 mg) **Day 22: Calaspargase pegol** 1500 and 1750 U/m^2 IV (Part 2)[b] **Days 1, 31: Methotrexate** 15 mg intrathecal **Days 1, 8, 29, 36: Rituximab** 375 mg/m^2 IV	**Days 1-28: Blinatumomab** 28 µg/day by IV continuous infusion, followed by a 14-day break. Cycles are 6 weeks long in total. It is recommended that all CD19-positive B-cell precursor ALL patients exhibiting MRD-positivity (MRD level of at least $\geq 10^{-3}$), receive 2 cycles of **blinatumomab** in between Interim Maintenance and Delayed Intensification. For MRD negative patients, it is recommended that 2 cycles of **blinatumomab** be given after consolidation, in between Interim Maintenance and Delayed Intensification, per Investigator discretion in eligible subjects. *At least 30 days between Day 22 of Interim Maintenance and Day 1 of Delayed Intensification.	**Days 1, 8, 15, 43, 50: Vincristine** 1.5 mg/m^2 (maximum dose 2mg) IV **Days 1-7, 15-21: Dexamethasone** 5 mg/m^2 PO or IV BID **Days 1, 8, 15: Doxorubicin** 25 mg/m^2 IV **Day 4 (or Day 5 or Day 6), 43: Calaspargase pegol** 1500 and 1750 U/m^2 IV (Part 2)[b] **Day 29: Cyclophosphamide** 1000 mg/m^2 IV **Days 29-32, 36-39: Cytarabine** 75 mg/m^2 IV or SC **Days 29-42: 6-Thioguanine** 60 mg/m^2 orally daily **Days 1, 29, 36: Methotrexate** 15 mg intrathecal **Days 1, 8, 29, 36: Rituximab** 375 mg/m^2 IV

[a]**Part 1 (Completed) Age/BMI Groups:**
- **Patients aged 22-39 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 2000 U/m^2 (n = 6)**
- **Patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 1500 U/m^2 (n = 4)**
- **Patients aged ≥ 55 years + BMI ≤ 35 kg/m^2 were treated with calaspargase pegol 1000 U/m^2 (n = 8)**
- **Patients aged < 55 years + BMI > 35 kg/m^2 were treated with calaspargase pegol 1000 U/m^2 (n = 8)**

[b]**Part 2 (Current) Age/BMI Groups:**
- **Patients aged 22-39 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1750 U/m^2**
- **Patients aged 40 to < 55 years + BMI ≤ 35 kg/m^2 will be treated with calaspargase pegol 1500 U/m^2**

After the Delayed Intensification phase, some patients may start the Maintenance Period before the end-of-treatment visit. See Section 6.4.7 for details.

4.1.2 Study Phases and Investigation Schedule

The study phases, which span from the Screening phase through the Long-Term Follow-up phase are summarized in Table (4.1.2) 1. The study start date is defined as the date of the first signed patient informed consent form (ICF). The study start date for each individual patient is the date of the signature of the informed consent. The expected duration of patient participation in the study will be approximately 12 to ≥ 18 months. Follow-up will continue for 2 additional years.

Table (4.1.2) 1 - Study Phases

Study Phase	Timing	Additional Details
Screening Phase	≤ 21 days of treatment initiation	Obtain informed consent/evaluate eligibility (see Section 5). Conduct all screening assessments (Table (4.1.2.1.1) 1). Limited steroids and a single dose of intrathecal cytarabine may be administered; systemic chemotherapy to begin ≤ 72 hours thereafter
Treatment Period - Remission Induction (RI; 35 days) - Remission Consolidation (56 days) - Interim Maintenance (56 days) - Delayed Intensification (DI; 56 days)	First calaspargase pegol dose in RI Day 4. Last study drug dose in Delayed Intensification Day 43	Administer calaspargase pegol and perform assessments per the study schedule (see Section 4.1.2) Treatment-emergent adverse events will be collected for 30 days after the last dose of the study drug in DI phase (see Section 8.9.1)
End-of-treatment (EOT) Visit	To occur 365 (± 7) days post first study drug dose in RI	Perform all evaluations listed in Table (4.1.2.5) 1
Early Discontinuation Visit	To take place 30 days (+1 or 2 days) after the last calaspargase pegol dose; may occur due to adverse events, induction failure, relapse etc (see Section 8.9 for adverse event reporting requirements).	- If early discontinuation occurs at a scheduled study visit, perform all evaluations for that visit (see Section 4.1.2 for all visit schedules) AND those for the end-of-treatment visit Table (4.1.2.5) 1. - A 30-day safety evaluation is required after last calaspargase pegol dose (see Section 8.9 for adverse event reporting requirements). - After early discontinuation, patients will be followed every 3 months until the 3-year post first calaspargase dose survival evaluation time point, except in case of a switch to alternate therapies or consent withdrawal
Long-Term Follow-up (LTFU) Phase	Starts after end of treatment or early discontinuation	Every 3 months phone call for disease/survival status assessment; no other data will be collected until the third year post-first calaspargase dose. Patients who discontinue calaspargase pegol treatment early and are switched to alternate therapies will not be included in long-term follow-up

Study Phase	Timing	Additional Details
Lost to Follow-up	Patients are considered lost to follow-up if attempts to contact them (see Section 5.8.3) are unsuccessful. The Investigator should document these attempts in the medical file.	
End of Study Definition	The end of the study is defined as the date of the end-of-treatment visit at 1 year of the last study participant, or the date of the last contact attempt if the last patient is declared lost to follow-up, whichever is later.	

***NOTE**: The Maintenance Period treatment cycle is administered per study CALGB 10403 treatment regimen at the physician's discretion and is **not part of the active treatment protocol**. Total duration of maintenance therapy is 2 years from the start of Interim Maintenance for female patients and 3 years from the start of Interim Maintenance for male patients.*

4.1.2.1 Screening and Remission Induction Phases

Written informed consent (see Section 13.3) will be obtained from each patient and/or his/her legal representative in the screening phase, before initiation of any study procedures. The screening phase will begin ≤ 21 days prior to treatment initiation, *i.e.*, start of protocol treatment in the induction phase. A screening visit will take place to evaluate patient eligibility for participation per the inclusion and exclusion criteria. The screening assessments are listed in Table (4.1.2.1.1) 1.

4.1.2.1.1 Pre-treatment

In the Screening Phase, limited treatment (≤ 7 days) with corticosteroids or hydroxyurea is allowed prior to protocol treatment administration in the Remission Induction phase.

A single dose of intrathecal (IT) cytarabine 70 mg IT may be given prior to treatment initiation, at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this IT therapy.

The Screening and Remission Induction schedule is provided in Table (4.1.2.1.1) 1.

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Table (4.1.2.1.1) 1 - Screening and Remission Induction Assessment Schedule

Assessment	Screening Phase ≤ 21 Days	Remission Induction Study Phase Day										Notes
		1	4 (or 5 or 6)	5	6	8	11	18	21	25	29	
Informed Consent and Patient Characteristics												
Informed consent	X											Before any study procedures are performed
Screening/non-screening criteria	X											
Inclusion/exclusion criteria	X											Within 7 days of inclusion
Demography	X											
Medical history	X											
Previous treatments	X											
Concomitant treatments	X	X	X	Throughout the study								Question patient about any changes in medications at every visit
Weight/Height*/body surface area/BMI	X		X									Pre-dose; at End-of treatment visit or Early Discontinuation *Height to be collected at Screening only for BSA calculation for dosing
Diagnostics/Medical Examination												
Physical examination	X		X									At screening within 7 days of inclusion; Pre-dose at induction; weekly or more frequently if clinically indicated thereafter
Vital signs	X		X									
Testicular examination	X											At screening within 7 days of inclusion; If clinical findings are equivocal, a biopsy is recommended.
ECOG PS	X		X									At screening within 7 days of inclusion. Details of assessment criteria are provided in Appendix 2
ECHO or MUGA	X											Within 7 days of inclusion (if performed within 42 days of treatment initiation, may not need to repeat at inclusion)
ECG	X											
Chest X-ray	X											
MRI/PET/CT scan	X											If relevant
Safety												
AE assessment		X	X	Throughout the study								Question patient about any changes at every evaluation
Hematology (CBC: Hematocrit, Hemoglobin, RBCs, WBCs; differential; platelets)	X		X				X	X			X	At screening within 7 days of inclusion; Pre-dose (the day of calaspargase pegol administration); then weekly (± 3 days) or more frequently if clinically indicated
Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin	X		X				X	X			X	

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Table (4.1.2.1.1) 1 (Cont'd) - Screening and Remission Induction Assessment Schedule

Assessment	Screening Phase ≤ 21 Days	Remission Induction Study Phase Day										Notes
		1	4 (or 5 or 6)	5	6	8	11	18	21	25	29	
Coagulopathy markers (PT-INR, aPTT, fibrinogen, D-dimer, and ATIII)	X (+ protein S activity)		X				X	X			X	At screening within 7 days of inclusion; Pre-dose (the day of calaspargase pegol administration). Twice weekly (± 2 days) while in-patient and at least once weekly (± 3 days) as outpatient, more frequently if clinically indicated
Liver function tests (ALT, AST, ALP, direct bilirubin and total bilirubin)	X (+ GGT)		X				X	X			X	
Glucose, amylase, lipase,	X		X				X	X			X	
Triglycerides	X		X									At screening within 7 days of inclusion Pre-dose the day of calaspargase pegol administration
Total cholesterol, HDL, LDL	X											At screening within 7 days of inclusion
PO_4, Uric Acid	X		X									At screening within 7 days of inclusion Pre-dose (the day of calaspargase pegol administration); then if abnormal value, perform weekly (± 3 days) until normal
LDH	X		X									At screening within 7 days of inclusion Pre-dose (the day of calaspargase pegol administration); then if abnormal value, perform weekly (± 3 days) until normal
Urinary analysis Macroscopic Panel (Dipstick)	X											Within 7 days of inclusion (see Section 8.2)
Hepatitis B (HBs antigen) and Hepatitis C (HCV antibody) testing	X											At screening only; within 7 days of inclusion
Pregnancy test	X (serum)		X (urine)									For women of childbearing potential only Within 7 days of inclusion at screening; Pre-dose on Day 4

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Table (4.1.2.1.1) 1 (Cont'd) - Screening and Remission Induction Assessment Schedule

Assessment	Screening Phase ≤ 21 Days	Remission Induction Study Phase Day										Notes
		1	4 (or 5 or 6)	5	6	8	11	18	21	25	29	
Asparaginase Activity/Pharmacokinetics/Immunogenicity												
PAA/PK/PD (blood sample)			X	X	X							Pre-dose on day of administration (within 4 hours before infusion start); 24, 48 hours post-dose (± 4 hours)
TDM							X	X		X		7, 14, and 21 days post-dose
Immunogenicity			X					X			X	Pre-dose, 14 days post-dose, at end of induction
Staging/Disease Assessment												
BMA/MRD (central and local testing)[a]	X										X	± 2 days; for central MRD one 2 mL BMA sample, first aspirate required for central testing. Local testing per institutional practice, and should be collected at the same time points whenever possible. A ± 2 day window for BMA sample collection for MRD central assessment is permitted as long as the patient has adequate blood count recovery after aplasia.
BMA/exploratory (central testing)[a]	X											2 mL BMA sample for exploratory analysis at screening phase. Refer to the section 9.4 of this protocol
Blood/MRD (central testing only)	X											4 mL blood sample for central testing, only in case of insufficient BMA provided there are sufficient numbers of circulating lymphoblasts (at least 1000/µL)
BMA immunophenotyping	X											Local testing
BMA cytogenetics/FISH (local testing)[a]	X										X*	Analysis per institutional practices. *At time of first CR (if diagnostic specimen is abnormal).
CSF cell count & cytospin exam	X	At all IT administrations										At Screening within 3 days of inclusion; Per NCCN guidelines (Clinical Practice Guidelines) and Investigator discretion; To be performed ± 3 days.
Investigational Medicinal Product Administration												
Calaspargase pegol administration			**X**									2-hour infusion; pre-medicate within 30 to 60 minutes prior to administration (see Section 6.1)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BMA = bone marrow aspiration; BSA = body surface area; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete remission; CSF = cerebrospinal fluid; CT = computerized tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Group performance status; FISH = fluorescence in situ hybridization; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NCCN = National Comprehensive Cancer Network; PAA = plasma asparaginase activity; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT-INR = prothrombin time and international normalized ratio; RBC = red blood cell; TDM = therapeutic drug monitoring; WBC = white blood cells.

[a]Further details on sample handling and analysis are provided in the Lab Manual. BMA for local MRD, FISH, and Cytogenetics assessments will be completed per institutional practices; however, as the results of local laboratory testing will be used for clinical decision making it is recommended that they be obtained at the same time points whenever possible.

4.1.2.2 Remission Consolidation

The Remission Consolidation schedule is provided in Table (4.1.2.2) 1.

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Table (4.1.2.2) 1 - Remission Consolidation Assessment Schedule

Assessment	Study Phase Day												Notes
	8	15	16	22	29	36	43	44	50	56	57	64	
Concomitant treatments	X	X	Throughout the study										Question patient about any changes in medications at every visit
Weight/body surface area		X					X						As specified; at end-of-treatment visit or early discontinuation.
Safety													
Physical examination		X					X						Pre-dose (the day of calaspargase pegol administration); weekly or more frequently if clinically indicated
Vital signs		X					X						
Hematology (CBC: Hematocrit, Hemoglobin, RBCs, WBCs; differential; platelets)	X	X		X	X	X	X		X		X		
Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin	X	X		X	X	X	X		X		X		Pre-dose (the day of calaspargase pegol administration); weekly (± 3 days) or more frequently if clinically indicated
AE assessment	X	X	Throughout the study										Question patient about any changes at every evaluation
ECOG PS		X					X						Details of assessment criteria are provided in Appendix 2
Coagulopathy markers (PT-INR, aPTT, fibrinogen, D-dimer, and ATIII)	X	X		X	X	X	X		X		X		Pre-dose (the day of calaspargase pegol administration); and twice weekly (± 2 days) while in-patient and at least once weekly (± 3 days) as outpatient, more frequently if clinically indicated
Liver function tests (ALT, AST, ALP, direct bilirubin and total bilirubin)	X	X		X	X	X	X		X		X		
Glucose, amylase, lipase	X	X		X	X	X	X		X		X		
Triglycerides		X					X						Pre-dose
Pregnancy test (urine)		X					X						Pre-dose; for women of childbearing potential only

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Table (4.1.2.2) 1 (Cont'd) - Remission Consolidation Assessment Schedule

Assessment	Study Phase Day												Notes
	8	15	16	22	29	36	43	44	50	56	57	64	
Asparaginase Activity/Pharmacokinetics/Immunogenicity													
PAA/PK/PD (blood sample)		X	X				X	X					Pre-dose on day of administration (within 4 hours before infusion start); 24 hours post-dose (± 4 hours)
TDM				X	X	X			X		X	X	7, 14, and 21 days post-dose
Immunogenicity		X					X						Pre-dose; required at all specified time points, or in case of premature end of treatment/study, at the end of treatment or at the study discontinuation
Immunogenicity		X					X						Pre-dose; required at all specified time points, or in case of premature end of treatment/study, at the end of treatment or at the study discontinuation
Staging/Disease Assessment													
BMA/MRD (central and local testing)[a]										X			± 2 days; one 2 mL BMA sample, first aspirate is required for central testing. Local testing per institutional practice A ± 2-day window for BMA sample collection for MRD central assessment is permitted as long as the patient has adequate blood count recovery after aplasia.
BMA cytogenetics/FISH (local testing)[a]										X*			Analysis per institutional practices. *At time of first CR (if diagnostic specimen is abnormal)
CSF cell count & cytospin exam	At IT administration												Per NCCN guidelines (Clinical Practice Guidelines) and Investigator discretion; To be performed ± 3 days.
Investigational Medicinal Product Administration													
Calaspargase pegol administration		**X**					**X**						2-hour infusion; pre-medicate within 30 to 60 minutes prior to administration (see Section 6.1)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BMA = bone marrow aspiration; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete remission; CSF = cerebrospinal fluid; ECOG PS = Eastern Cooperative Group performance status; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; NCCN = National Comprehensive Cancer Network; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; PT-INR = prothrombin time and international normalized ratio; RBC = red blood cell; TDM = therapeutic drug monitoring; WBC = white blood cells

[a] *Further details on sample handling and analysis are provided in the Lab Manual.*

4.1.2.3 Interim Maintenance

The Interim Maintenance schedule is provided in Table (4.1.2.3) 1.

Table (4.1.2.3) 1 - Interim Maintenance Assessment Schedule

Assessment	Study Phase Day															Notes
	1	2	3	9	11	16	21	22	23	29	31	36	38	41	43	
Concomitant treatments	Throughout the study															Question patient about any changes in medications at every visit
Weight/body surface area								X								As specified; at end-of-treatment visit or early discontinuation.
Safety																
Physical examination								X								Pre-dose (the day of calaspargase pegol administration); weekly or more frequently if clinically indicated
Vital signs								X								
Hematology (CBC: Hematocrit, Hemoglobin, RBCs, WBCs; differential; platelets)		X		X		X		X		X		X			X	Pre-dose (the day of calaspargase pegol administration); weekly (± 3 days) or more frequently if clinically indicated
Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin		X		X		X		X		X		X			X	
AE assessment	Throughout the study															Question patient about any changes at every evaluation
ECOG PS								X								Details of assessment criteria are provided in Appendix 2
Coagulopathy markers (PT-INR, aPTT, fibrinogen, D dimer, and ATIII)		X		X		X		X		X		X			X	Pre-dose (the day of calaspargase pegol administration) and twice weekly (± 2 days) while in-patient and at least once weekly (± 3 days) as outpatient, more frequently if clinically indicated
Liver function tests (ALT, AST, ALP, direct bilirubin, and total bilirubin)		X		X		X		X		X		X			X	
Glucose, amylase, lipase		X		X		X		X		X		X			X	
Triglycerides								X								Pre-dose
Pregnancy test (urine)								X								Pre-dose; for women of childbearing potential only

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Table (4.1.2.3) 1 (Cont'd) - Interim Maintenance Assessment Schedule

Assessment	Study Phase Day															Notes
	1	2	3	9	11	16	21	22	23	29	31	36	38	41	43	
Asparaginase Activity/Pharmacokinetics/Immunogenicity																
PAA/PK/PD (blood sample)								X	X							Pre-dose on day of administration (within 4 hours before infusion start); 24 hours post-dose (± 4 hours)
TDM										X		X			X	7, 14, and 21 days post-dose
Immunogenicity								X								Pre-dose; required at all specified time points, or in case of premature end of treatment/study, at the end of treatment or at the study discontinuation
Staging/Disease Assessment																
CSF cell count & cytospin exam	At IT administrations															Per NCCN guidelines (Clinical Practice Guidelines) and Investigator discretion
Investigational Medicinal Product Administration																
Calaspargase pegol administration								**X**								2-hour infusion; pre-medicate within 30 to 60 minutes prior to administration (see Section 6.1)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BMA = bone marrow aspiration; BUN = blood urea nitrogen; CBC = complete blood count; CSF = cerebrospinal fluid; ECOG PS = Eastern Cooperative Group performance status; IT = intrathecal; NCCN = National Comprehensive Cancer Network; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; PT-INR = prothrombin time and international normalized ratio; RBC = red blood cell; TDM = therapeutic drug monitoring; WBC = white blood cells

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4.1.2.4 Delayed Intensification

The Delayed Intensification schedule is provided in Table (4.1.2.4) 1.

Table (4.1.2.4) 1 - Delayed Intensification Assessment Schedule

Assessment	Study Phase Day													Notes
	4	5	11	18	25	29	32	39	43	44	50	57	64	
Concomitant treatments	Throughout the study													Question patient about any changes in medications at every visit
Weight/body surface area	X								X					As specified; at the end-of-treatment visit or early discontinuation.
Safety														
Physical examination	X								X					Pre-dose (the day of calaspargase pegol administration); weekly or more frequently if clinically indicated
Vital signs	X								X					
Hematology (CBC: Hematocrit, Hemoglobin, RBCs, WBCs; differential; platelets)	X		X	X	X		X	X	X		X	X	X	Pre-dose (the day of calaspargase pegol administration); weekly (± 3 days) or more frequently if clinically indicated
Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium, and corrected calcium), ammonia, total protein, albumin	X		X	X	X		X	X	X		X	X	X	
AE assessment	Throughout the study													Question patient about any changes at every evaluation
ECOG PS	X								X					Details of assessment criteria are provided in Appendix 2
Coagulopathy markers (PT, INR, aPTT, fibrinogen, D-dimer, and ATIII)	X		X	X	X		X	X	X		X	X	X	Pre-dose (the day of calaspargase pegol administration); and twice weekly (± 2 days) while in-patient and at least once weekly (± 3 days) as outpatient, more frequently if clinically indicated
Liver function tests (ALT, AST, ALP; direct bilirubin, and total bilirubin)	X		X	X	X		X	X	X		X	X	X	
Glucose, amylase, lipase	X		X	X	X		X	X	X		X	X	X	
Triglycerides	X								X					Pre-dose
Pregnancy test (urine)	X								X					Pre-dose; for women of childbearing potential only

Table (4.1.2.4) 1 (Cont'd) - Delayed Intensification Assessment Schedule

Assessment	Study Phase Day													Notes
	4	**5**	**11**	**18**	**25**	**29**	**32**	**39**	**43**	**44**	**50**	**57**	**64**	
Asparaginase Activity/Pharmacokinetics/Immunogenicity														
PAA/PK/PD (blood sample)	X	X							X	X				Pre-dose on day of administration (within 4 hours before infusion start); 24 hours post-dose (± 4h)
TDM			X	X	X						X	X	X	7-, 14-, and 21-days post-dose
Immunogenicity	X								X					Pre-dose; required at all specified time points, or in case of premature end of treatment/study, at the end of treatment or at the study discontinuation
Staging/Disease Assessment														
BMA/MRD (central and local testing)[a]											X			± 2 days; one 2 mL BMA sample, first aspirate required for central testing. Local testing per institutional practice. A ± 2-day window for BMA sample collection for MRD central assessment is permitted as long as the patient has adequate blood count recovery after aplasia.
BMA cytogenetics/FISH (local testing)[a]											X*			Analysis per institutional practices. *At time of first CR (if diagnostic specimen is abnormal)
CSF cell count & cytospin exam	At IT administration													Per NCCN guidelines (Clinical Practice Guidelines) and Investigator discretion; To be performed ± 3 days.
Investigational Medicinal Product Administration														
Calaspargase pegol administration	**X**								**X**					2-hour infusion; pre-medicate within 30 to 60 minutes prior (see Section 6.1)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BMA = bone marrow aspiration; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete remission; CSF = cerebrospinal fluid; ECOG PS = Eastern Cooperative Group performance status; FISH = fluorescence in situ hybridization; IT = intrathecal; MRD = minimal residual disease; NCCN = National Comprehensive Cancer Network; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; PT-INR = prothrombin time and international normalized ratio; RBC = red blood cell; TDM = therapeutic drug monitoring; WBC = white blood cells

[a]*Further details on sample handling and analysis are provided in the Lab Manual.*

4.1.2.5 End-of-treatment Visit/Early Discontinuation Visit

The end-of-treatment visit will take place at 365 (± 7) days after the initial calaspargase dose at the Remission Induction phase, except in the case of early withdrawal. The end-of-treatment visit assessments are listed in Table (4.1.2.5) 1.

Conduct an Early Discontinuation visit with the patient 30 days (+1 or 2 days) after the last investigational medicinal product (IMP, calaspargase pegol) dose (see Section 8.9). Continue to obtain all study-required hematology, biochemistry, PAA, therapeutic drug monitoring (TDM), and immunogenicity samples and perform all protocol evaluations until the Early Discontinuation visit takes place.

For further practical details, methods of measurements are provided in Sections 7 and 8.

Residual blood samples will be kept until the US Food and Drug Administration (FDA) review process of the study results will be concluded.

The total volume of blood collected per participant, for the requirements of the study, is expected to be approximately 859 mL.

Table (4.1.2.5) 1 - End-of-treatment/Early Discontinuation Visit Assessments

Concomitant Treatments and Medical Examination - Concomitant treatments - Physical examination - Weight/BSA - Vital signs - ECOG PS - AE assessment **Hematology** (CBC: Hematocrit, Hemoglobin, RBCs, WBCs, differential, platelets) **Coagulation tests** (PT, INR, aPTT, fibrinogen, D-dimer, and ATIII) **Biochemistry** - Liver function tests (AST, ALT, ALP, GGT, direct bilirubin, and total bilirubin); - Glucose, amylase, lipase - LDH - Uric acid - Triglycerides, total cholesterol, HDL, LDL - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium, phosphate), ammonia, total protein, albumin. **Urinalysis** Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, Protein). If the dipstick test is at least 2+ on 1 or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s)	**Pregnancy Test** - Pregnancy test for women of childbearing potential (urine) **Other Investigations** - ECHO or MUGA - ECG - Immunogenicity (at the end of treatment or at treatment and study discontinuation) **Disease Assessment (made per Investigator's discretion)** - BMA/MRD (central and local testing, if applicable) - BMA immunophenotyping (local testing) - BMA cytogenetics/FISH (local testing) - CSF cell count & cytospin exam if clinically indicated (Results from most recent IT result may be used) - BMA/exploratory (central testing) – refer to the Section 9.4

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BMA = bone marrow aspiration; BSA = body surface area; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete remission; CSF = cerebrospinal fluid; CT = computerized tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Group performance status; FISH = fluorescence in situ hybridization; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; INR = international normalized ratio; IT = intrathecal; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MUGA = multiple-gated acquisition; PT = prothrombin time; RBC = red blood cell; WBC = white blood cells

4.1.3 Part 1: Dose Confirmation

Although Part 1 of this study has completed, for protocol continuity, the details of this part of the study are included in this section. Please see Section 4.1.4 for Part 2 Expansion.

Dose confirmation was to be conducted in Part 1 in each of the 4 patient groups, with at least 3 evaluable patients in each cohort; the completed Part 1 dose groups and final enrollment in each group are summarized in Table (4.1.3) 1.

Table (4.1.3) 1 - Part 1 Dose Groups and Final Enrollment

Population	Calaspargase pegol starting doses	Final Enrollment
Young adults aged 22 to 39 years and BMI ≤ 35 kg/m²	2000 U/m^2	6
Adults aged 40 to < 55 years and BMI ≤ 35 kg/m²	1500 U/m^2	4
Adults aged ≥ 55 years and BMI ≤ 35 kg/m²	1000 U/m^2	8
Adults aged < 55 years and BMI > 35 kg/m^2		8

BMI = body mass index

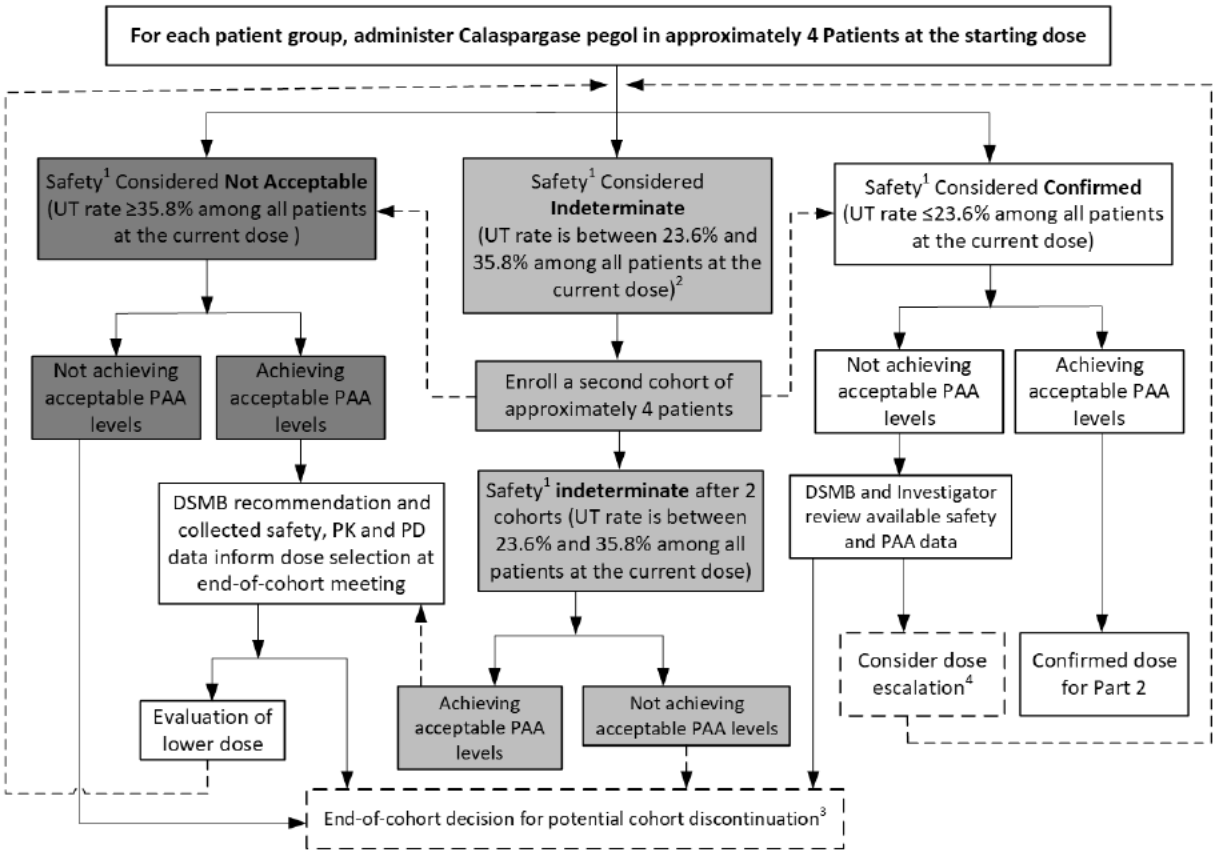
An evaluable patient was defined as a patient who received calaspargase pegol at the starting dose in Remission Induction phase and had all toxicity data for 30 days after that dose. Patients discontinued for AEs not listed in Table (4.1.3.3) 1, Criteria for Defining Unacceptable Toxicities, and for reasons other than unacceptable toxicity (UT), were considered non-evaluable and were to be replaced.

All patient groups were enrolled simultaneously. Cohort expansion to approximately 4 additional patients per cohort and evaluation for dose adjustment was to be made at the end-of-cohort meetings guided by Data Safety Monitoring Board (DSMB) recommendations and all available safety and PAA data.

Dose confirmation was based primarily on safety assessment of the starting dose for each patient group. Starting dose safety was categorized as not acceptable, indeterminate or acceptable based on the observed rate of UT compared with a prespecified threshold range (see additional details in Section 4.1.3.1.2). The decision to adjust the dose was based on the accumulated safety and PAA data (see Section 4.1.3.2) and in consult with the DSMB at an end-of-cohort meeting (see Section 4.1.3.3).

The dose confirmation process is summarized in Figure (4.1.3) 1. Note that the dose was not confirmed in Part 1 of this study, but recommended for Part 2, as the 22-39 age group dosing was reduced to 1750 U/m^2, and this dose was not confirmed. In addition, patients ≥ 55 years of age and patients with BMI > 35 kg/m^2 will not be enrolled into Part 2.

Figure (4.1.3) 1 - Dose Confirmation Run-in Procedure



[1] The safety boundary (23.6%) and toxicity boundary (35.8%) are calculated based on BOIN design. UT rate js calculated for UT-evaluable patients.

[2] A dose will not be considered as the recommended dose for Part 2 if safety is not considered acceptable after 2 run-in cohorts.

[3] DSMB recommendation, investigator input, and all available safety and PAA data will be considered for the end-of-cohort decision.

[4] Dose escalation may be considered if appropriate based on PAA levels and modeling along with safety, with no intolerable toxicity.

DSMB = Data Safety Monitoring Board; PAA = plasma asparaginase activity; PD = pharmacodynamics; PK = pharmacokinetics; UT = unacceptable toxicity

Note: The dose was not confirmed in Part 1 of this study, but recommended for Part 2, as the 22-39 age group dosing was reduced to 1750 U/m^2, and this dose was not confirmed. In addition, patients ≥ 55 years of age and patients with BMI > 35 kg/m^2 will not be enrolled into Part 2.

4.1.3.1 Safety Evaluation

4.1.3.1.1 Starting Doses

The starting doses for each age group in completed Part 1 (Table (4.1.3) 1) were 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 the 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.

4.1.3.1.2 Dosage Safety Classification Method

Although the Part 1 run-in period is not strictly a dose-finding phase, we borrowed certain considerations from the Bayesian optimal interval design (BOIN) (Yuan et al, 2016) to inform recommendations based on safety evaluation. Approximately 4 patients were enrolled in each run-in patient cohort in Part 1. At the end of each run-in cohort, the recommendation to confirm safety or deescalate in subsequent cohorts was based on the proportion of UT-evaluable patients experiencing any UT at the tested dose and pre-specified safety and toxicity boundaries. The target toxicity rate was set as $\phi = 30\%$, and the safety boundary of 23.6% and toxicity boundary of 35.8% were calculated based on the default under-dosing toxicity rate $\phi_1 = 0.6\phi$ and overdosing toxicity rate $\phi_2 = 1.4\phi$, respectively. The proportion of patients achieving PAA ≥ 0.1 U/mL was also used to confirm the tested dose through population PK modeling based-predictions accumulating PAA data from previous pediatric studies and each run-in cohort (see Section 4.1.3.2).

If the observed UT rate at the tested dose fell below the safety boundary of 23.6% (i.e., UT rate ≤ 23.6%) and at least 3 safety-evaluable patients were treated and the predicted proportion of patients achieving PAA ≥ 0.1 U/mL was considered sufficient, this dose was considered as confirmed. Further dose escalation was not recommended based on the safety evaluation recommendation; however, dose escalation would be considered if PD data and population PK modeling indicated that dose escalation was appropriate. If PAA was below the target level, all available safety and PAA data, as well as DSMB recommendation and Investigator input were considered for deciding whether dose escalation was appropriate or feasible.

If the observed UT rate fell between the safety and toxicity boundaries, the rule recommended expanding the tested dose for further safety evaluation regardless of PAA data; patients in the next run-in cohort was to be treated at the same dose with additional PAA data obtained. If UT rate from the 2 cohorts at this dose was ≤ 23.6%, safety of the dose was to be confirmed, and the dose may be confirmed provided PAA data were acceptable. In the event UT was > 23.6%, no further cohort expansion took place at the current dose. The DSMB recommendation and all available data were considered for a decision to discontinue this dose or de-escalate.

If the observed UT rate at the tested dose fell above the toxicity boundary of 35.8% (i.e., UT rate ≥ 35.8%), the dose was considered intolerable, and dose reduction was considered for the subsequent cohort provided predictions of the proportion of patients achieving PAA ≥ 0.1 U/mL were acceptable. Dose reduction was supported by PD data and population PK modeling to ensure appropriate PAA levels. Approximately 4 patients were to be enrolled at the reduced dose for further safety evaluation. If predicted PAA at the reduced dose was below the target level, discontinuation of this cohort was considered.

Recommendations for actions based on UT consideration under various scenarios are provided in Table (4.1.3.1.2) 1. A maximum of 2 run-in cohorts were enrolled for any dose. The final decision was based on safety (including long-term safety), PK, PD, DSMB recommendations, Investigator input, and other related considerations.

Table (4.1.3.1.2) 1 - Dose Confirmation/Escalation and De-escalation Recommendation given number of Unacceptable Toxicities and number of Evaluable Patients at the Current Dose

Recommendation based on UT consideration	Number of Evaluable Patients Treated at the Current Dose					
	3	**4**	**5**	**≥ 6**	**7**	**8**
Confirm safety and allow escalation if Number of UTs	0	0	≤ 1	≤ 1	≤ 1	≤ 1
De-escalate if number of UTs	≥ 2	≥ 2	≥ 2	≥ 3	≥ 3	≥ 3

UT = unacceptable toxicity

4.1.3.2 Pharmacokinetics/Pharmacodynamics Assessment for Dose Evaluation

Plasma asparaginase activity collected through 30 days after the induction Day 4 dose of each run-in cohort was used for PD assessment. The proportion of patients at the tested dose achieving PAA ≥ 0.1 U/mL was predicted through a population PK modeling approach. The prior population PK model built on asparaginase activity data from 2 large, randomized trials with Asparlas in the pediatric population (AALL07P4 and DFCI 11-001) was used to perform these predictions, that was adjusted on the level of plasma asparaginase activity observed in each run-in cohort if relevant. These predictions, along with safety, supported the decision on the appropriateness of the dose for the next run-in cohort if needed, and then for Part 2.

4.1.3.3 Unacceptable Toxicity Definition

Unacceptable toxicity (UT) assessments were provided in Part 1 only for dose confirmation for Part 2. A UT was defined as a clinically significant AE following the first administration of calaspargase pegol, considered by the Investigator as related to the test drug and that met any of the criteria included in Table (4.1.3.3) 1. For all UTs except hypersensitivity, the UT assessment period was defined as within 30 days after the initial calaspargase pegol administration in the Remission Induction phase. As antibody-mediated hypersensitivity events have been reported to occur at the time of the second or third asparaginase dose (in Studies DFCI 11-001 and AALL07P4), the assessment period for hypersensitivity UT only was extended from the initial calaspargase pegol administration at Remission Induction through and inclusive of the day of the third calaspargase pegol dose expected to occur on Day 43 of the Remission Consolidation phase (may occur later in the event of delayed/skipped dose).

This safety evaluation was performed for each patient enrolled in any of the 4 dose confirmation groups in Part 1 of the study. Patients who discontinued within the UT evaluation period for reasons not classified as UTs were not evaluable for safety confirmation in Part 1.

A TEAE for which a causal relationship to the test drug was evidently ruled out (an AE related to disease progression, intercurrent illness, or concomitant medications) was not considered a UT.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

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Table (4.1.3.3) 1 - Criteria for Defining Unacceptable Toxicities

Toxicity	Unacceptable Toxicity Criteria (CTCAE v5)	Evaluation Period
Hypersensitivity	Grade ≥ 3 hypersensitivity. Grade 3 hypersensitivity is corresponding to allergic/ anaphylactic reaction, characterized by symptomatic bronchospasm, with or without urticaria; or allergy-related edema/angioedema; or hypotension AND requiring corrective parenteral treatment by IV antihistamines, cortisone, or adrenaline.	For Grade ≥ 3 hypersensitivity UT, only the UT evaluation period extends from the initial dose at Remission Induction through the third calaspargase pegol dose expected to occur on Day 43 of Remission Consolidation (or later in the event of delayed/skipped dose) see Section 4.1.3.3. If a patient is discontinued before the third dose, the patient will be considered to have completed the hypersensitivity reactions UT assessment and will be evaluable for UT assessment.
Liver toxicity	AST or ALT increase Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline, if baseline was abnormal) and does not subside to ≤ Grade 2 AND leads to a ≥ 28-day delay of the next scheduled cycle of chemotherapy or leads to permanent discontinuation of calaspargase pegol.	For all UTs except hypersensitivity, the UT assessment period is defined as within 30 days after the initial calaspargase pegol administration in the Remission Induction phase.
	Direct bilirubin ≥ 3.1 mg/dL and does not subside to < 2 mg/dL AND leads to a ≥ 28-day delay of the next scheduled cycle of chemotherapy, or requires permanent discontinuation of calaspargase pegol	
Pancreatic toxicity	Pancreatitis Grade ≥ 3 (clinical pancreatitis)	
Hemorrhage	Non-CNS hemorrhage Grade ≥ 4	
	Any CNS bleeding Grade ≥ 3	
Thromboembolic events	Grade ≥ 3 pulmonary embolism, intracardiac thrombus, CNS thrombosis	
	Any Grade 4 thromboembolic event	
	Note: Catheter-associated thromboembolic events of any grade will not be considered as UTs	
Other AEs	Any other AE Grade ≥ 3 related to the test drug (except those rapidly correctable and deemed by the Investigator to be not clinically important) may be considered a UT by the Investigator. *Grade ≥ 3 or ≥ 4 laboratory abnormalities other than those mentioned above will not constitute a UT unless accompanied by clinically impactful symptomatology.*	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; DSMB = Data Safety Monitoring Board; IV = intravenous; ULN = upper limit of normal; UT = unacceptable toxicity

See Section 8.11 for the management of the above-mentioned toxicities.

4.1.3.4 Data Safety Monitoring Board

During Part 1, regular DSMB meetings occurred to ensure safety oversight. All safety data collected during the UT observation period after the induction dose were provided. In addition, all available safety data accumulated for each patient participating in Part 1 were reviewed by the DSMB. The DSMB recommendations were considered for all decisions for dose confirmation, escalation or reduction.

4.1.3.5 End-of-cohort Meeting

After having tested 1 dose level and before including patients to test a new dose level, an end-of-cohort meeting was conducted, which included representatives of the Sponsor, including clinical, safety, biostatistics, clinical PK, and pharmacometrics departments and the study Investigators, including the Principal Investigator, to obtain a joint decision on the next dose level based on:

- The dose proposed by the Bayesian method (based on unacceptable toxicities).
- All safety data.
- PK/PD data (PAA), along with PK modeling based-predictions of PAA.
- DSMB recommendation, including whether a sufficient number of patients were enrolled in each cohort before proceeding to Part 2.
- Investigator input.

4.1.3.6 Completion of Part 1

Upon completion of Part 1, all safety and PAA data through 21 days after the calaspargase pegol dose at Day 43 in Remission Consolidation phase were analyzed for these 2 dose groups. No further enrollment in each of these 2 dose groups were to take place in Part 1 once the required number of patients for dose confirmation was reached for each of them.

In addition, all available safety and PAA data (through 21 days post dose in Remission Consolidation) for patients ≥ 55 years of age and those with BMI > 35 kg/m^2 were evaluated; however, enrollment of patients in these dose groups was to continue in Part 1 until the specified number of patients or dose confirmation was reached.

Based on all available data after Part 1, the recommended dose for each age group may be adjusted. The clinical assumption and the threshold may be updated taking into consideration the observed PAA data in adults, along with the clinical assumptions based on the observed PAA data in the pediatric studies with calaspargase pegol.

During the conduct of Part 1 of this study, in cohorts with adults age < 55 years and BMI > 35kg/m^2, one patient experienced an event of intraparenchymal hemorrhage and sinus venous thrombosis, and another patient had a pulmonary embolism. Additionally, in cohorts with adults age ≥ 55 years and BMI ≤ 35 kg/m^2, one patient had Grade 3 embolic stroke and hyperbilirubinemia, and another had Grade 3 hypersensitivity. These events were considered unacceptable toxicities that were considered related to calaspargase pegol. The Sponsor informed the DSMB of these unacceptable toxicities and thromboembolic events. Dose adjustments for patients aged 22-39 years + BMI < 35 kg/m^2 are implemented in Part 2 (Section 4.1.4).

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4.1.4 Part 2: Expansion

Because Part 1 of this study has been completed, Part 2 of the study is now being conducted.

During the conduct of Part 1 of this study, in cohorts with adults age < 55 years and BMI > 35kg/m^2, one patient experienced an event of intraparenchymal hemorrhage and sinus venous thrombosis, and another patient had a pulmonary embolism. Additionally, in cohorts with adults age ≥ 55 years and BMI ≤ 35 kg/m^2, one patient had Grade 3 embolic stroke and hyperbilirubinemia, and another had Grade 3 hypersensitivity. These events were considered unacceptable toxicities that were considered related to calaspargase pegol. The Sponsor informed the DSMB of these unacceptable toxicities and thromboembolic events. Dose adjustments for patients aged 22-39 years + BMI < 35 kg/m^2 are implemented in Part 2.

Patients enrolling into Part 2 will receive calaspargase pegol according to the age/BMI categories in Table (4.1.4) 1.

Table (4.1.4) 1 - Calaspargase pegol Doses for Part 2

Population	Calaspargase pegol Doses
Adults aged 22 to 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

BMI = body mass index

4.2 Measures to Minimize Bias

This is an open-label single arm study without randomization.

During the study:
- Analysis of samples of PAA and TDM will be performed in a specific central laboratory which will minimize the variability of measurements.
- Samples for immunogenicity (ADA, anti-PEG antibodies) will be sent to a specific analytical center for analyses, to also minimize the variability of measurement.

4.3 Study Products and Blinding Systems

This is an open-label study. No study medication blinding is required.

4.3.1 Products Administered

Calaspargase pegol is the investigational medicinal product (IMP), which will be manufactured by Servier Pharmaceuticals LLC (Boston MA, USA). The other backbone chemotherapies and elective treatments are considered as non-investigational medicinal product (NIMPs).

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

Table (4.3.1) 1 - Description of the Investigational Medicinal Product (Calaspargase pegol)

Pharmaceutical form	solution for infusion
Unit dosage	3750 U/5 mL vial
Appearance, color	Clear, colorless solution
Composition	Each vial contains 750 U calaspargase pegol active ingredient per mL, monobasic sodium phosphate and dibasic sodium phosphate as buffering agent, sodium chloride for tonicity and water for injections quantum satis (q.s.) to 1 mL as solvent

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

Table (4.3.1) 2 - Investigational Medicinal Product Packaging

Number of units of the pharmaceutical form per primary packaging	3750 U calaspargase pegol/5 mL solution for infusion in an individual clear glass vial
Number of primary packaging per secondary packaging	1 vial of calaspargase pegol liquid per box
Number of secondary packaging per patient and per treatment period	The number of calaspargase pegol vials per administration will depend on the BSA of the patient

BSA = body surface area

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

4.3.2 Investigational Medicinal Product Management

The IMP will be distributed to the investigational centers from a United States central depot. The IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to Section 6.5), accountability and collection are the responsibility of the Investigator and/or pharmacist of the medical institution. Specific handling conditions are described in the Pharmacy Manual.

4.3.2.1 Stability and Storage of the Investigational Medicinal Product

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

The Investigator/pharmacist is responsible for daily IMP temperature monitoring using FONT-CIRT-FORM-311 "Drug kit temperature log sheet - center" (recording Min-Max temperature every working day) or an equivalent document. This form and detailed instructions regarding storage and handling of study medication are provided in the Pharmacy Manual.

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 enter and complete in real time in Randomization and Trial Supply Management (RTSM) and all the documents provided by the Sponsor concerning IMP management

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. The Investigator will notify the monitor of all complaints set out by a participant (*e.g.*, 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 center.

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4.3.2.2 Destruction of Unused Investigational Medicinal Product

All unused IMP will be destroyed. Destruction of the IMP is the responsibility of the Sponsor and the country depot subcontracted or the pharmacist of the medical institution. Remaining treatments (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 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 center. An IMP collection and destruction form will be completed before the shipment of IMP to destruction. Destruction of IMP may be possible (after drug accountability and Sponsor authorization) when the product has expired or after at least the last visit of the last treated participant.

4.3.3 Non-investigational Medicinal Products

The backbone therapies (NIMPs) are supplied by the individual clinical centers. Their use is detailed in Section 6 with additional drug information, including adverse event profile and drug interactions provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

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 Coordinator, the Sponsor or the Investigator/Coordinator or the DSMB or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the Coordinator. The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued, the on-going patients 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 patient's interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the Sponsor, the DSMB, the IRB/IEC, and Competent Authorities.

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(s) and sufficient notice is given in advance of the intended termination.

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Reason for 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 IRB/IEC or local Competent Authorities, the Sponsor procedures, or Good Clinical Practice (GCP) guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

The IRB/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

Local laboratory reports and local imagery performed will be considered as source documents. Source data and source documents will be those generated by investigational sites (centers) and other contributors, they will be kept as electronic or as written records. There are no data to be recorded directly on the electronic case report form (e-CRF) (*i.e.*, without any prior written or electronic record of data). Source data and source documents of the center should be clearly identified in a specific, detailed and signed document before the beginning of the study.

Patients' medical files (*e.g.*, electrocardiogram [ECG] report, clinical laboratory examinations reports, tumor assessment reports and all other patient examinations results) will be considered as source documents.

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5 SCREENING AND WITHDRAWAL OF PARTICIPANTS

Screening evaluation will take place within 3 weeks (≤ Day -21) prior to treatment initiation once the patient or legally authorized representative gives informed consent and signs the ICF. Informed consent must be obtained before completing any study specific procedures. Laboratory or diagnostic evaluations that are part of standard care and performed prior to informed consent may be used to determine patient eligibility provided they were performed within the 21-day screening window. Diagnostic or imaging evaluations, such as ECG, multiple-gated acquisition (MUGA)/echocardiogram (ECHO), x-ray, or ultrasound of uninvolved organs that are not used for tumor measurement may be acceptable, if obtained within 42 days of initiation of treatment in Remission Induction. Laboratory evaluations should be performed within 7 days before inclusion. If more than 1 set of laboratory results are available, the more recent results will be used for eligibility assessment.

Patients who are unable to complete or meet certain eligibility criteria at the initial screening may be permitted to be re-screened once (see Section 5.6). If re-screening is performed within the original 21-day screening window, no new ICF will be required, and only evaluations that did not originally meet the eligibility criteria will be repeated. If re-screening is done beyond the original 21-day screening window, the patient will be re-consented and all required screening procedures will be repeated.

5.1 Screening Criteria

5.1.1 Demographic Characteristics

1.a Male or female patients aged ≥ 22 years and < 55 at the time of informed consent.

5.1.2 Medical and Therapeutic Criteria

2.a Patients with cytologically confirmed and documented Philadelphia-negative, B-cell or T-cell ALL according to current NCCN guideline (Clinical Practice Guidelines) and WHO classification (Arber et al, 2016; Terwilliger et al, 2017).

- Diagnosis of ALL requires demonstration of ≥ 20% bone marrow lymphoblasts upon hematopathology review of bone marrow aspirate and biopsy materials (see Section 7.2.3 for additional details).

3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2.
4. Able to understand study requirements and comply with study procedures.

5.1.3 Informed Consent

5. Written informed consent obtained prior to any study specific procedure.

5.2 Non-screening (Non-selection) Criteria

5.2.1 General Criteria

6. Participation in another interventional study at the same time or within 14 days or at least 5 half-lives of the study drug(s) (whichever is longer) prior to the first IMP administration; participation in non-interventional registries or epidemiological studies is allowed.

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5.2.2 Medical and Therapeutic Criteria

7. Down Syndrome (due to the likelihood of excessive toxicity with treatment).
8. Prior treatment with chemotherapy or radiotherapy related to studied disease except for limited treatment (≤ 7 days) with corticosteroids or hydroxyurea and a single dose of IT therapy:
   - Single-dose IT cytarabine is allowed prior to inclusion or prior to initiation of systematic therapy for patient's convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this IT therapy.
   - Patients who are being treated with chronic steroids for other reasons than the study disease (*e.g.*, asthma, autoimmune disorders, lupus) are eligible.
9. No prior therapy for ALL (including prior surgery or bone marrow transplant) except emergency therapy (corticosteroids or hydroxyurea) for blast cell crisis, superior vena cava syndrome, or renal failure due to leukemia infiltration of the kidneys.
   - When indicated, leukapheresis or exchange transfusion is recommended to reduce the white blood cell (WBC) count.
10. Psychiatric illness/social situation that would limit compliance with study requirements.
11. Treatment with hormones, other chemotherapeutic agents (not protocol therapy) or any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint are not permitted.
    - Except for steroids given for adrenal failure, insulin for diabetes, and intermittent use of dexamethasone as an antiemetic.
12. Pregnancy and/or lactation (or planning to become pregnant in near future).
13. Known history of non-gallstone-related pancreatitis.
14. Known severe hepatic impairment:
    - direct bilirubin > 3 x upper limit of normal (ULN) (unless suspected leukemic involvement of the liver[3]
    - ALT/AST > 5 times ULN (unless suspected leukemic involvement of the liver[1]).
15. Known history of coagulopathy (*e.g.*, hemophilia and know protein S deficiency).

16.a Active thromboembolic event(s) (*i.e.,* symptomatic despite initiation of anti-coagulation therapy), or history of CNS thromboses.

17. Active uncontrolled infection.
18. Adequate cardiac function to receive anthracycline, per the opinion of the Investigator.
19. Any other medical condition which in the opinion of the Investigator likely to jeopardize the patient's safety or to interfere with the conduct of the study.

20.a Currently active second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

21. History of sensitivity to PEG or PEG-based drugs.
22. Prior treatment with L-asparaginase products.

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[3] *Suspected leukemic involvement of the liver per investigator judgement; must be documented*
Calaspargase pegol will be administered when both bilirubin and ALT/AST are consistent with Grade ≤ 2 per CTCAE v5 (use ULN of the normal laboratory reference range, not the patient's baseline value):
- *direct bilirubin < 2 mg/dL; or total bilirubin > 1.5 to 3 x ULN*
- *ALT/AST > 3.0 to 5 x ULN*

The study Principal Investigator may be consulted if there are questions about initiating treatment.

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5.3 Inclusion Criteria

All screening criteria must still be fulfilled at the time of the inclusion visit.

5.3.1 Medical and Therapeutic Criteria

23. Adequate renal function based on the last assessment performed within 7 days prior to inclusion defined as:
    - Creatinine clearance ≥ 50 mL/min, assessed as glomerular filtration rate (GFR) using the modification of diet in renal disease (MDRD) or Cockcroft & Gault formula (Appendix 3; according to local practice).

5.4 Exclusion Criteria

All non-selection criteria must still be fulfilled at the time of the inclusion visit. Note that exclusion criteria 29, 30, and 31 were implemented with protocol Amendment 4 after the completion of Part 1.

5.4.1 Medical and Therapeutic Criteria

24. Philadelphia chromosome-positive, Burkitt's leukemia, mixed lineage/mixed phenotype acute leukemia, and acute undifferentiated leukemia (AUL) per the WHO classification (2016).
25. Women of childbearing potential tested positive in a pregnancy test (within 7 days prior to inclusion).
26. Any other laboratory abnormality likely to jeopardize the patient's safety.
27. Patients with Hepatitis B (positive for HBs antigen), and Hepatitis C (HCV antibody) at inclusion.
28. Participants known to be human immunodeficiency virus (HIV)-positive are excluded. HIV testing is not required prior to enrollment.
29. BMI > 35 kg/m^2*
30. Age ≥ 55 years*
31. Pre-existing history of hepatic veno-occlusive disease

*Note: Patients whose BMI increases to 35 kg/m^2 or higher, 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 when considering continued participation.

5.5 Definition of Women of Childbearing Potential and Contraception Methods

5.5.1 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.

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5.5.2 Contraception Methods

5.5.2.1 Definition of Highly Effective Contraception Methods

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 (intravaginal or transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (intravaginal or transdermal), 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 sterilisation (vasectomy).

5.5.2.2 Definition of Acceptable Contraception Methods for the Study

Acceptable contraception methods for the study are those considered as highly effective methods. Participants using a hormonal contraceptive must also use a second method of contraception (barrier method) such as, male or female condom with or without spermicide, cap, diaphragm, or sponge with spermicide.

WOCBP must use a highly effective method of birth control during the study and until at least 6 months after the last dose of IMP.

Since there is a potential indirect interaction between calaspargase pegol and oral contraceptives, the concomitant use of calaspargase pegol and oral contraceptive is not recommended. Thus, another method must be used for women of childbearing potential.

Male participants with women of childbearing potential 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.

5.6 Retest Management During Screening Period

A participant 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 participant previous results or medical history and if she/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 participant will not be required to sign another informed consent, and the original participant identification number will be used.

In any case, the last results available for each parameter must be considered for the patient at inclusion.

5.7 Additional Information Recorded at the Screening/Inclusion Visit

Not applicable.

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5.8 Premature Discontinuation of the Investigational Medicinal Product

5.8.1 Withdrawal Criteria

A participant may be withdrawn from the study at any time for any reason (*e.g.*, lost to follow-up, withdrawal of consent, AE). Premature discontinuation of IMP does not mean that the participant prematurely stops the participation in the study (see Section 5.8.1.2). Patients with suspected leukemic involvement of the liver and high bilirubin and ALT/AST values at enrolment will be withdrawn from the study and replaced if they do not meet the criteria for IMP administration and do not receive study treatment.

5.8.1.1 Temporary Investigational Medicinal Product Discontinuation

Criteria for temporary IMP discontinuation are provided in Table (8.11) 1 in Section 8.11 (Management of Treatment Dose Adaptations due to Toxicities).

5.8.1.2 Permanent Premature Investigational Medicinal Product Discontinuation

Patients who prematurely and permanently discontinue IMP will remain on study unless they withdraw consent and discontinue the study. 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 the efficacy and safety evaluation of all participants who received calaspargase pegol.

The reasons for premature discontinuation of calaspargase pegol are:

- **AEs** incompatible with continuation of the calaspargase pegol according to the judgment of the Investigator and/or or according to the criteria defined in Section 8.11.
- **Pregnancy** (for reporting see Section 8.9.2.3).
- **Major protocol deviation** if it interferes with the study evaluations and/or if it jeopardizes participant's safety, *e.g.*, any medical event requiring administration of an unauthorized concomitant treatment (see Section 6.6).
- **Progressive disease** documented with appropriate method of evaluation according to disease characteristics. One of the following conditions are to be considered as progressive disease:
- Failure to achieve CR with persistence of leukemia cells after treatment.
- Patients not eligible for the Remission Consolidation phase due to his/her bone marrow status M (*e.g.,* ≥ M3 [> 25% blasts]) on Day 29 at the end of the Remission Induction phase.
- An increase of at least 25% in the absolute number of circulating or bone marrow leukemic blasts.
- Development of extramedullary disease.
- **Non-medical reason** (*e.g.*, consent withdrawal, participant's removal).
- **Silent inactivation of asparaginase activity**, determined according to the therapeutic drug monitoring samples and the decision tree provided in Section 6.1.3.
- **Other, physician decision** (for reasons that cannot be included in any of the criteria listed above).

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5.8.2 Procedure to Follow if a Participant Prematurely Discontinues IMP

Upon discontinuation of study treatment, the Investigator must:
- Notify the Clinical Research Associate immediately.
- Indicate the main reason, if there are several reasons.
- Record this information in the e-CRF.
- Continue to obtain all required study samples and perform all study evaluations until the Early Discontinuation visit.
- Conduct an Early Discontinuation visit with the patient, 30 days after the last IMP dose.
- All evaluations planned for the Early Discontinuation visit will be completed (Section 4.1.2.5).
- All prematurely discontinued patients who received at least one dose of calaspargase pegol will be followed every 3 months through the Long-Term Follow-Up Phase for disease and survival assessment, unless the patient withdraws consent or switches to alternative therapies. The total duration of long-term follow-up will be approximately 2 years, for a total of 3 years after the initial calaspargase pegol administration.

In the case of premature discontinuation from the study due to an AE (regardless of whether the AE requires immediate notification), 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 e-CRF which concerns AEs. If the Investigator cannot collect the information from a visit, he must collect it from the patient's treating physician ensuring the follow-up of the participant.

If the study is stopped/calaspargase pegol is discontinued as a result of an event requiring immediate notification, the procedure described in Section 8.9.2.5 is to be implemented.

The dispositions to be taken after the IMP discontinuation are described in Section 6.8.

5.8.3 Lost to Follow-up

When the Investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc.), to establish the reason for the discontinuation of calaspargase pegol and to suggest the participant comes to an End-of-Treatment visit. The Investigator may consult public registries in accordance with local regulations and privacy requirements. If all these attempts to contact the participant fail, the Investigator can then declare the participant "lost to follow-up." The Investigator should document all these attempts in the corresponding medical file.

5.8.4 Interruption or Discontinuation of Non-investigational Medicinal Products

All questions regarding treatment delays or permanent treatment discontinuation should be addressed to the study Principal Investigator.

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6 TREATMENT OF PARTICIPANTS

Calaspargase pegol will be administered along with a multi-agent chemotherapy regimen based on the CALGB 10403 study (cytarabine, dexamethasone, vincristine, daunorubicin, and methotrexate). The timing of therapy administration is provided in Figure (4.1.1) 1 and discussed in detail below in Section 6.4.3. Calaspargase pegol will be administered at Remission Induction, Remission Consolidation, Interim Maintenance, and Delayed Intensification phases. Maintenance phase treatment will be consistent with the CALGB 10403 treatment regimen. There are data to support the use of rituximab in addition to chemotherapy for CD20-positive patients (Clinical Practice Guidelines). For CD20-positive patients only rituximab IV will be administered in the post-induction treatment phases (Section 6.4.3). Additional drug information on the backbone therapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

6.1 Calaspargase pegol (Investigational Medicinal Product)

The calaspargase pegol dose is calculated according to body surface area (BSA). The BSA will be calculated by using the DuBois formula (Du Bois et al, 1989) (all BSA calculations are rounded to 2 decimal places):

$$\text{BSA } (m^2) = ([\text{Body Weight (kg)}]^{0.425} \times [\text{Height (cm)}]^{0.725}) \times 0.007184$$

Study sites are required to use the same scale throughout the study. Dose capping at 1 vial is not permitted. Consult the Pharmacy Manual for additional details.

During Part 2, calaspargase pegol will be administered IV at different dose levels depending on patient's age and BMI (Table (6.1) 1). Part 1 (completed) dose groups and final enrollment are described in Table (4.1.3) 1.

Table (6.1) 1 - Calaspargase pegol Dose Levels Part 2

Population	Calaspargase pegol doses
Adults aged 22 to 39 years and BMI ≤ 35 kg/m²	1750 U/m²
Adults aged 40 to < 55 years and BMI ≤ 35 kg/m²	1500 U/m²

BMI = body mass index

6.1.1 Premedication

The following prophylaxis and management measures should be implemented to minimize the risk of hypersensitivity or other infusion-related reactions:

Before each calaspargase pegol administration (30 to 60 minutes prior), patients will be pre-medicated with 650 mg acetaminophen, 100 mg hydrocortisone (hydrocortisone is optional if patients are receiving dexamethasone on the same day as calaspargase pegol in a given treatment course) and 25 to 50 mg diphenhydramine (or equivalent).

6.1.2 Calaspargase pegol Infusion

Calaspargase pegol will be administered as a 2-hour infusion. Detailed instructions for calaspargase pegol administration are provided in the Pharmacy Manual.

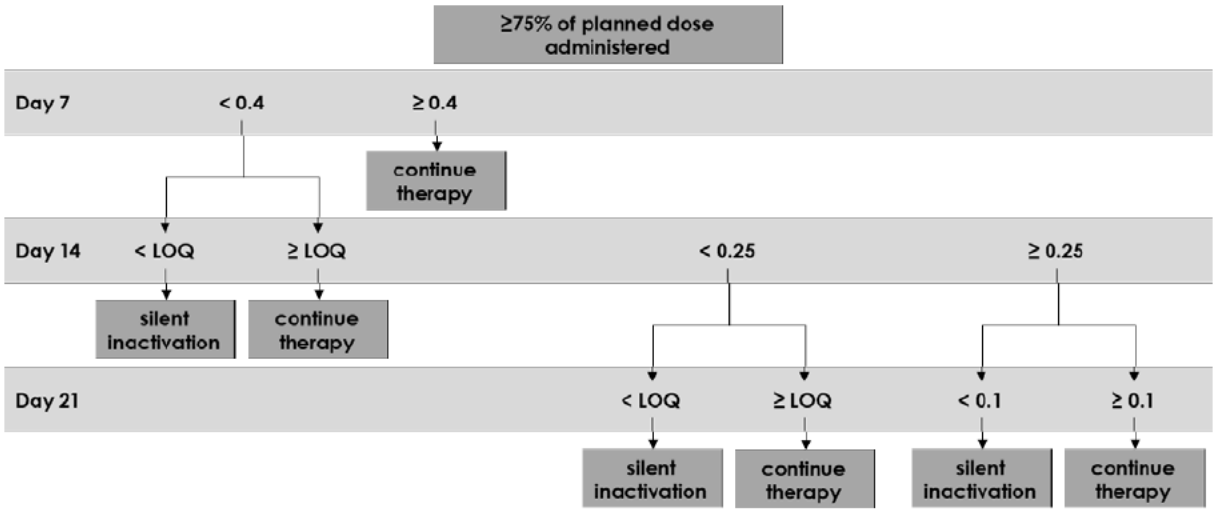
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6.1.3 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) for PAA will be performed at 7, 14, and 21 days post each calaspargase pegol dose in each treatment phase (Remission Induction, Remission Consolidation, Interim Maintenance, and Delayed Intensification). This evaluation will be performed at a central laboratory and the results will be available to Investigators in real time. The sampling, handling, and processing details are provided in the laboratory manual.

Silent inactivation of asparaginase activity is determined based on the TDM samples, using two consecutive samples, according to the algorithm in Figure (6.1.3) 1. If the evaluation of TDM leads to the conclusion of a silent inactivation, the patient may be switch to an alternative therapy at the investigator's discretion and the sponsor should be notified. A prerequisite for the evaluation of the TDM is that the patient has received at least 75% of the planned dose; otherwise, the presence of silent inactivation cannot be determined. Two consecutive TDMs with asparaginase activity levels below the limit of quantification (LOQ) results in determination of a silent inactivation. Other scenarios with different thresholds of asparaginase activity (in U/mL) that would lead to the determination of a silent inactivation are indicated in the Figure (6.1.3) 1.

Figure (6.1.3) 1 - Algorithm for Asparaginase Activity Monitoring and Determination of Silent Inactivation



PAA values expressed in U/mL
LOQ: 0.045 U/mL

6.1.4 Dose Adaptations Due to Toxicity

For treatment dose adaptations due to toxicities, please refer to Table (8.11) 1 in Section 8.11 (Management of Treatment Dose Adaptations due to Toxicities).

6.2 Non-investigational Medicinal Products

The backbone regimen drugs will be administered according to the schedule based on that used in the CALGB 10403 protocol (see Figure (4.1.1) 1). In addition, rituximab will be used for CD20+ subjects as specified in Section 6.4.3. They will be considered NIMPs and will not be provided by the Sponsor.

A single dose of IT cytarabine is allowed prior to enrolment or prior to initiation of systemic therapy for patient's convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. If IT cytarabine is administered prior to study enrolment, systemic chemotherapy must begin within 72 hours of this IT therapy.

It is acceptable for individual chemotherapy doses to be delivered within a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new course/cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday.

Every effort should be made to administer all chemotherapy agents on the day specified in the protocol. However, a window of ± 2 days will allow for weekends, holidays, and any developments in the patient's medical condition that preclude administration on the day specified. The reason for using the window should be captured in the source documents.

Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (*e.g.*, serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

6.2.1.1 Use of Rituximab and Blinatumomab in Eligible Subjects

Please See Appendix 4 for detailed information for rituximab (for all CD20+ patients as defined by CD20 levels of expression in accordance to the NCCN guidelines) and blinatumomab (Litzow et al, 2022).

6.2.1.2 Rituximab

In adults with CD20-positive, Ph-negative, B-cell ALL, the addition of rituximab to the pediatric-inspired GRAALL protocol improved both EFS and OS. In addition, the MD Anderson Cancer Center treated 97 patients with de novo CD20-positive Philadelphia-chromosome negative B-cell ALL with rituximab at 375 mg/m^2/dose during the first 4 courses of the hyper-CVAD regimen (R-hyper-CVAD; rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with cytarabine and methotrexate). The results demonstrated an improved 3-year CR duration, a lower relapse rate and an improved OS, but only in younger patients under the age of 60 years as compared to historical controls (Maury (a) et al, 2015; Thomas et al, 2010). Additional studies also have shown that addition of rituximab to ALL chemotherapy protocol regimens containing asparaginase, improved outcomes for adults with CD20-positive, Philadelphia-chromosome-negative B-cell ALL (Wieduwilt et al, 2018; Rangel-Patiño et al, 2023; Shi Z et al, 2022; Maury (b) et al, 2016).

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A National Comprehensive Cancer Network (NCCN) panel recommends that induction therapy for AYA patients with Ph-negative ALL, should comprise multiagent chemotherapy that includes a rituximab regimen (Clinical Practice Guidelines). For patients <65 years of age and without substantial comorbidities, the NCCN panel-recommended treatment approach is similar to that for AYA patients. Induction therapy should comprise multiagent chemotherapy, that includes rituximab (for CD20-positive disease) and hyper-CVAD with or without rituximab (NCCN Guidelines v2.2024).

6.2.1.3 Blinatumomab

MRD persistence after consolidation chemotherapy indicates chemotherapy resistance and is the most important risk factor for hematologic relapse in ALL. The BLAST trial was an open-label, single-arm study in adults with B-cell precursor ALL in hematologic complete remission with MRD (> 10^{-3}). All patients received blinatumomab at a dose of 15 mg/m^2 per day by continuous IV infusion for up to 4 cycles. Eighty-eight of 113 evaluable patients (78%) achieved a complete MRD response (Gökbuget et al, 2018). This has led to the initial FDA approval of blinatumomab for patients with persistent MRD after standard chemotherapy, defined as a level greater than 10^{-3}.

Blinatumomab was approved on June 14, 2024 in CD19-positive Philadelphia chromosome-negative B-cell precursor acute ALL in the consolidation phase of multiphase chemotherapy.

This approval was based on efficacy data from Study E1910 and Study 20120215.

In Study E1910, eligible patients in hematologic complete remission (CR) or CR with incomplete peripheral blood count recovery (CRi) following induction and intensification chemotherapy were randomized 1:1 to receive a consolidation regimen comprised of multiple blinatumomab monotherapy cycles plus multiple cycles of intensive chemotherapy (blinatumomab arm) or to intensive chemotherapy alone (chemotherapy arm). The major efficacy outcome measure was overall survival (OS). The 3-year OS was 84.8% (95% CI: 76.3, 90.4) and 69% (95% CI: 58.7, 77.2) in the blinatumomab and chemotherapy arms, respectively. The hazard ratio [HR] for OS was 0.42 [95% CI: 0.24, 0.75] p-value 0.003). In a later analysis with a median follow-up of 4.5 years, the 5-year OS was 82.4 % [95% CI (73.7, 88.4)] in the blinatumomab arm and 62.5 % [95% CI (52.0, 71.3)] in the chemotherapy arm. The hazard ratio was 0.44 [95% CI (0.25, 0.76)].

In Study 20120215, pediatric and young adult patients with Ph-negative BCP ALL were randomized 1:1 to receive blinatumomab or the IntReALLHR2010 HC3 intensive combination chemotherapy as the third consolidation cycle. The major efficacy outcome measures were OS and relapse-free survival (RFS). The 5-year OS was 78.4% (95% CI: 64.2, 87.4) and 41.4% (95% CI: 26.3, 55.9) in the blinatumomab and chemotherapy arms, respectively (OS HR 0.35 [95% CI: 0.17, 0.70]). The 5-year RFS was 61.1% (95% CI: 46.3, 72.9) and 27.6% (95% CI: 16.2, 40.3) in the blinatumomab and chemotherapy arms, respectively (RFS HR 0.38 [95% CI: 0.22, 0.66].

6.2.1.3.1 Blinatumomab Dosing and Administration

Blinatumomab will be permitted for CD19-positive Philadelphia chromosome-negative B-ALL patients. To ensure consistent treatment for patients participating in the trial, the sponsor recommends that all eligible CD19-positive Philadelphia chromosome-negative B-ALL patients receive blinatumomab, unless the investigator does not think this is clinically advisable for the patient. Patients that did not receive blinatumomab may remain on study and continue

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protocol therapy. Patients with MRD positivity who received blinatumomab, but do not have the option to proceed to transplant due to lack of a suitable match or there are clinical contraindications also may remain on study and continue protocol therapy. If hematopoietic stem cell transplantation (HSCT) or any other non-protocol treatments are indicated, aside from blinatumomab, the patient will be discontinued from the study. If patients receive blinatumomab, 2 cycles should be administered between Interim Maintenance and Delayed Intensification (Figure (4.1.1) 1).

There should be at least 30 days between administration of Day 22 Interim Maintenance Calaspargase pegol dose and the start of the first dose of blinatumomab (Figure (4.1.1) 1). An optional dose of intrathecal methotrexate may be given between the 2 cycles of blinatumomab if determined necessary by the investigator. The sponsor and the principal investigator should be consulted prior to administering this additional dose. Reasons for the additional intrathecal methotrexate dose will be documented.

Please always refer to the current Blinatumomab USPI label. Blinatumomab is administered by package insert guidelines. A single cycle of blinatumomab treatment consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days). Patients weighing 45 kg or more receive a fixed-dose. For patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA). Please refer to Blinatumomab USPI label regarding updated dosing information and suggested number of days patients should be observed in the hospital during administration. The Blinatumomab USPI label has also been updated and now includes the risk of immune effector cell neurotoxicity syndrome (ICANS). The most recent updated prescribing information regarding neurotoxicity monitoring and management and administration instructions is located in Appendix 4, but the most current blinatumomab USPI should be considered.

6.3 Prior to Initiation of Therapy

Patients must be evaluated for CNS and testicular (where applicable) disease at diagnosis.

6.3.1 Central Nervous System Involvement at Diagnosis

The CNS disease classification method is presented in Table (6.3.1) 1.

Table (6.3.1) 1 - Determination of Central Nervous System Leukemia

Classification	Characteristics
CNS1	CSF has < 5 WBC/µL with cytospin negative for blasts; or ≥ 10 RBC/µL with cytospin negative for blasts.
CNS2	CSF has < 5 WBC/µL with cytospin positive for blasts; or ≥ 10 RBC/µL with cytospin positive for blasts; or ≥ 10 RBC /µL, WBC/µL ≥ 5 but less than Steinherz/Bleyer algorithm with cytospin positive for blasts (see below).
CNS3[1]	CSF has ≥ 5 WBC/µL with cytospin positive for blasts; or ≥ 10 RBC/µL, ≥ 5 WBC/µL and positive by Steinherz/Bleyer algorithm (see below); or clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome).

CNS = central nervous system; CSF = cerebrospinal fluid; RBC = red blood cell; WBC = white blood cell
[1] CNS3 patients who achieve a CR will receive 18 Gy cranial radiation therapy during the first cycle of Maintenance Therapy

Steinherz/Bleyer Method of Evaluating Initial Traumatic Lumbar Punctures

If the patient has leukemia cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL with blasts, the following algorithm should be used to define CNS disease:

CSF WBC	> 2X	Blood WBC
CSF RBC		Blood RBC

For example: A patient with cerebrospinal fluid (CSF) WBC ≥ 5/µL with blasts whose CSF WBC/RBC is greater than twice the blood WBC/RBC ratio has CNS disease at diagnosis. If the CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC = 46,000/µL; blood RBC = 3 x 10^6/µL

CSF WBC: 60/µL	= 0.04, and is	> 2X	Blood WBC: 46,000/µL	= 0.015
CSF RBC: 1500/µL			Blood RBC: 3 x 10^6/µL	

6.3.2 Testicular Involvement at Diagnosis

Unilateral or bilateral testicular enlargement should be assessed. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass. Patients with clinical evidence of testicular disease at diagnosis and persisting at the end of induction therapy will receive radiation to the testes during consolidation therapy (see Appendix 6).

6.3.3 Prior to Remission Induction

The following will be performed according to Investigator judgment:

- Begin allopurinol at a dose of 300 mg/day (unless allergic) and continue until peripheral blasts and extramedullary disease are reduced. In some situations, it may be appropriate to use rasburicase.
- Prior to starting Remission Induction phase, patients should be hydrated at 2400 to 3000 mL/day to maintain urine output > 100 mL/hour until peripheral blasts and extramedullary disease are reduced. Use of D5W with or without sodium bicarbonate is recommended.
- Prior to starting Remission Induction, it is recommended to start prophylactic ursodiol (ursodeoxycholic acid; Actigall®) at a dose of 300 mg three times per day and continue throughout Remission Induction.

6.3.4 Infection Prophylaxis

The following will be performed according to Investigator's discretion and institutional guidelines:

- During Remission Induction only, neutropenic and anti-fungal prophylaxis is highly recommended with a fluoroquinolone and micafungin.
- Beginning with Remission Induction, patients should receive herpes simplex and zoster prophylaxis with acyclovir at a dose of 400 mg three times daily or valacyclovir at 500 mg twice daily.
- Beginning with Remission Consolidation, all patients should receive one tablet of double strength trimethoprim/sulfamethoxazole (cotrimoxazole) three days per week continuing throughout therapy and for 6 months post-completion of therapy. For patients allergic to or experiencing excessive myelosuppression with cotrimoxazole, alternative prophylactic

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regimens include dapsone, atovaquone, or aerosolized pentamidine (300 mg once every 4 weeks via nebulizer). In some settings IV pentamidine may be considered.

- Recommended (not required, please follow institutional guidelines): For those patients who have not had chicken pox, zoster immune globulin should be given within 72 to 96 hours of exposure to varicella or herpes zoster. Give 1 vial (125 units/vial) per 10 kg, rounded up to next vial (maximum 5 vials). Continue chemotherapy as scheduled. If varicella or zoster develops, discontinue chemotherapy until infection resolves and treat with IV acyclovir or equivalent antiviral agent.
- Recommended (not required, please follow institutional guidelines): For those patients who have not been exposed to measles, immune globulin 0.5 mL/kg intramuscularly (IM, maximum dose 15 mL) should be given up to 6 days following measles exposure. Alternatively, patients may receive 400 mg/kg intravenous immunoglobulin (IVIG) up to 6 days following exposure.

6.4 Therapeutic Regimen

6.4.1 Pre-treatment

Limited treatment (≤ 7 days) with corticosteroids or hydroxyurea is allowed in the screening phase prior to initiation of study protocol treatment in Remission Induction phase.

A single dose of IT cytarabine 70 mg IT may be given prior to treatment initiation, at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this IT therapy.

6.4.2 Remission Induction Therapy

All patients will undergo Remission Induction therapy. The Remission Induction therapeutic regimen is presented in Table (6.4.2) 1. Detailed instructions are included below. Additional drug information on the backbone therapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

Table (6.4.2) 1 - Remission Induction Therapeutic Regimen

Administration Day	Therapy
1	Cytarabine 70 mg IT
1 – 7; 15 – 21	Dexamethasone 5 mg/m^2 PO or IV BID (twice a day). Do not taper.
1, 8, 15, and 22	Vincristine 1.5 mg/m^2 IV. (Maximum dose 2 mg)
	Daunorubicin 25 mg/m^2 IV
4 (or 5 or 6)	Calaspargase pegol (dose per Table (6.1) 1)
8, 29	Methotrexate 15 mg IT (also administered on Days 15 and 22 for patients with CNS3)

IT = intrathecal; IV = intravenous; PO = oral

IT Cytarabine 70 mg IT total dose on Day 1 (may be given prior to enrollment for patient's convenience, for example at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture). Patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy to enhance drug delivery to the head. CSF will be sent for cell count and cytospin exam. If administered prior to study enrollment, systemic chemotherapy must begin within 72 hours of this IT therapy.

Dexamethasone 5 mg/m^2 orally (PO) or IV, twice daily (BID) on Days 1 – 7 and 15 – 21. Do not taper. Round to nearest 1 to 2 mg dose.

Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 8, 15, and 22. Voriconazole and posaconazole should be used with caution with vincristine.

Daunorubicin 25 mg/m^2 IV on Days 1, 8, 15, and 22.

Calaspargase pegol 1500 – 1750 U/m^2 IV (Age 22 to 39: 1750 U/m^2; Age 40 to < 55: 1500 U/m^2) **x 1 dose** on Day 4 (**OR Day 5 OR Day 6)**. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone (hydrocortisone is optional if patients are receiving dexamethasone on the same day as calaspargase pegol in a given treatment course) and 25 to 50 mg diphenhydramine (or equivalent) 30 to 60 minutes prior to calaspargase pegol.

Calaspargase pegol will be administered as a 2-hour infusion. Detailed instructions for calaspargase pegol administration are provided in the Pharmacy Manual.

The calaspargase pegol dose is calculated according to BSA. The BSA will be calculated by using the DuBois formula (Du Bois et al, 1989) (all BSA calculations are rounded to 2 decimal places) (Stewart et al, 2016). Dose capping at 1 vial is not permitted.

IT-Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) total dose on Day 8 and 29. For patients with CNS3 also give on Days 15 and 22. Patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy to enhance drug delivery to the head. Send CSF for cell count and cytospin exam.

Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

A bone marrow aspirate for all patients on Day 29 to assess induction response and MRD. Bone marrow M status will be evaluated according to the definition provided in Table (6.4.2) 2. Note that a bone biopsy is not needed unless it's a part of a site's standard practice. If a biopsy is obtained, the results should be entered onto the eCRF.

Table (6.4.2) 2 - Bone Marrow M Status Definitions

Rating	Blast Cells (%)[1]
M0	0 – 5.0
M1	0 – 5.0
M2	5.1 – 25.0
M3	> 25.0 – 50.0
M4	> 50.0

1. *The term "blast cell" includes any cell that cannot be classified as a more mature normal element, and includes "leukemic cells," pathologic lymphocytes, and stem cells.*

Patients with bone marrow M status: M3 or M4 (greater than 25% lymphoblasts) will not be eligible for the Remission Consolidation phase and will have to discontinue the study. Another treatment option will be proposed by the Investigator.

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6.4.3 Remission Consolidation Therapy

All patients will undergo Remission Consolidation therapy. The Remission Consolidation therapeutic regimen is presented in Table (6.4.3) 1. Detailed instructions are included below.

Additional drug information on the backbone therapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

Table (6.4.3) 1 - Remission Consolidation Therapeutic Regimen

Administration Day	Therapy
1, 29	Cyclophosphamide 1000mg/m^2 IV
1-4, 8-11, 29-32, and 36-39	Cytarabine 75 mg/m^2 IV or SC
1-14, 29-42	6 mercaptopurine 60 mg/m^2 orally
15, 22, 43, and 50	Vincristine 1.5 mg/m^2 IV. (Maximum dose 2 mg)
15, 43	Calaspargase pegol (dose per Table (6.1) 1)
1, 8, 15, and 22	Methotrexate 15 mg IT (omit Days 15, 22 for patients with CNS3)
1, 8 and 29, 36	Rituximab 375 mg/m^2 IV (for CD20+ patients only)

IT = intrathecal; IV = intravenous; SC = subcutaneous

Consolidation therapy will begin within 7 days after peripheral blood counts recover with absolute neutrophil count (ANC) ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, the study Principal Investigator should be contacted. Therapy should be interrupted for patients who are febrile, neutropenic and proven infected, and resumed at the same point when the signs of infection have abated. Otherwise, therapy should not be interrupted for myelosuppression alone, except on Day 29. **Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL**.

Patients with clinical evidence of testicular disease at diagnosis that does not resolve completely by the end of induction should receive radiation to testes during consolidation therapy (see Appendix 6).

Cyclophosphamide 1000 mg/m^2 IV on Day 1 and Day 29. It is recommended to reduce urine specific gravity to ≤ 1.015 prior to administering cyclophosphamide. Give IV fluids to maintain urine output. Furosemide may be used (0.25 – 0.5 mg/kg/dose IV) for urine output < 3 mL/kg/hour after cyclophosphamide administration.

Cytarabine 75 mg/m^2 IV or subcutaneously (SC) on Days 1 – 4 (*i.e.*, 4 doses), 8 – 11, 29 – 32, and 36 – 39.

6-Mercaptopurine (6-MP): 60 mg/m^2 PO on Days 1 – 14 and 29 – 42. Give 6-MP at least 1 hour after evening meal. 6-MP is not to be taken with milk or citrus products. Adjust dose using 50 mg tablets and different doses on alternating days in order to attain weekly cumulative dose as close as possible to 420 mg/m^2/week. Do not escalate dose based on blood counts during this course. Round to nearest 25 mg dose. See Appendix 4 for details.

Vincristine 1.5 mg/m^2 (maximum 2 mg) IV once per week on Days 15, 22, 43, and 50. Voriconazole and posaconazole should be used with caution with vincristine.

Calaspargase pegol 1500 – 1750 U/m^2 IV (Age 22 to 39: 1750 U/m^2; Age 40 to < 55: 1500 U/m^2) on Days 15 and 43. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25 to 50 mg diphenhydramine (or equivalent) 30 to 60 minutes prior to calaspargase pegol.

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Calaspargase pegol will be administered as a 2-hour infusion. Detailed instructions for calaspargase pegol administration are provided in the Pharmacy Manual.

The calaspargase pegol dose is calculated according to BSA. The BSA will be calculated by using the DuBois formula (Du Bois et al, 1989) (all BSA calculations are rounded to 2 decimal places) (Stewart et al, 2016). Dose capping at 1 vial is not permitted.

IT-Methotrexate 15 mg IT total dose (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Days 1, 8, 15, and 22 **[omit Day 15 and 22 for CNS3 patients].** Patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy to enhance drug delivery to the head. Send CSF for cell count and cytospin exam.

Rituximab (for CD20+ patients only, as defined by CD20 levels of expression in accordance to the NCCN guidelines and as defined in Section 6.2.1.2): 375 mg/m^2 IV on Days 1 and 8 and Days 29 and 36. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent).

Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

6.4.3.1 Bone Marrow Examination

A bone marrow aspirate must be obtained for all patients at Day 56 of the consolidation phase to assess for continuing remission status. Note that a bone biopsy is not needed unless it's a part of the site's standard practice. If a biopsy is obtained, the results should be entered onto the eCRF.

6.4.3.2 Radiation Therapy

All patients with clinical evidence of testicular disease at diagnosis that does not resolve completely by the end of induction therapy will receive testicular irradiation during consolidation. Testicular irradiation should start during consolidation and must be completed before the end of consolidation.

6.4.4 Interim Maintenance Therapy

The Interim Maintenance therapeutic regimen is presented in Table (6.4.4) 1. Detailed instructions are included below. Additional drug information on the backbone therapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

Table (6.4.4) 1 - Interim Maintenance Therapeutic Regimen

Administration Day	Therapy
1, 11, 21, 31, and 41	Methotrexate at the starting dose of 100 mg/m^2 IV escalated by 50 mg/m^2/dose
	Vincristine 1.5 mg/m^2 IV (Maximum dose 2 mg)
22	Calaspargase pegol (dose per Table (6.1) 1)
1, 31	Methotrexate 15 mg IT
1, 8 and 29, 36	Rituximab 375 mg/m^2 IV (for CD20+ patients only)

IT = intrathecal; IV = intravenous

Begin Interim Maintenance within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the Principal Investigator for the study. Therapy should be interrupted for patients with severe infections and resumed when the signs of infection have abated.

Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 11, 21, 31, and 41. Voriconazole and posaconazole should be used with caution with vincristine.

IV-Methotrexate (starting dose 100 mg/m^2 IV) on Days 1, 11, 21, 31, and 41. (Treating physicians should discuss patients with pleural effusions with the Principal Investigator before initiating methotrexate therapy.) **Obtain blood counts prior to each dose of methotrexate. If the ANC > 750/µL and platelets > 75,000/µL, then escalate the IV- methotrexate (MTX) dose by 50 mg/m^2 for each subsequent dose.** For example, the Day 11 dose would be 150 mg/m^2. **Cap dose at 200 mg/m^2.** If a delay is necessary, then see the instruction for dose modifications.

Missed doses of methotrexate will not be made up. Cotrimoxazole should not be given on same day as methotrexate.

Otherwise, therapy should not be interrupted for simple myelosuppression. It is suggested to avoid weekend treatment by alternating Mon-Tue with Thu-Fri with 9 to 11 days between doses.

If a patient develops renal failure subsequent to the administration of IV methotrexate, obtain a serum methotrexate level and administer leucovorin. Leucovorin will not reverse renal toxicity but will minimize or prevent further toxicity to bone marrow and mucosal cells from delayed excretion. Leucovorin should be continued until the methotrexate level is < 0.1 µM. Hemodialysis is not very effective for resolving renal damage; oral charcoal, bile drainage, induced emesis, etc., have also been tried but are not very effective. To prevent this complication, adequate fluid intake (IV or PO ≥ 3000 mL/day) is indicated, with alkalinization (pH > 7) of urine using $NaHC0_3$. Diamox may be used to supplement $NaHC0_3$ alkalinization of the urine. Since MTX readily enters body fluids, patients with effusion(s) can have sustained high levels and must be monitored carefully.

Calaspargase pegol 1500 – 1750 U/m^2 IV (Age 22 to 39: 1750 U/m^2; Age 40 to < 55: 1500 U/m^2) on Days 22. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25 to 50 mg diphenhydramine (or equivalent) 30 to 60 minutes prior to calaspargase pegol.

Calaspargase pegol will be administered as a 2-hour infusion. Detailed instructions for calaspargase pegol administration are provided in the Pharmacy Manual.

The calaspargase pegol dose is calculated according to BSA. The BSA will be calculated by using the DuBois formula (Du Bois et al, 1989) (all BSA calculations are rounded to 2 decimal places) (Stewart et al, 2016).

IT-Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) total dose on Days 1 and 31. To enhance drug delivery to the head, patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy. Send CSF for cell count and cytospin exam.

Rituximab (for CD20+ patients only, as defined in Section 6.2.1.2): 375 mg/m^2 IV on Days 1 and 8 and Days 29 and 36. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent).

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Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

6.4.5 Blinatumomab Therapy Between Interim Maintenance and Delayed Intensification

Please see Section 6.2.1.3.1 for applicable dosing and administration information.

Please always refer to the current Blinatumomab USPI label. Blinatumomab is administered by package insert guidelines.

6.4.6 Delayed Intensification Therapy

The Delayed Intensification therapeutic regimen is presented in Table (6.4.6) 1. Detailed instructions are included below. Additional drug information on the backbone therapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

Table (6.4.6) 1 - Delayed Intensification Therapeutic Regimen

Administration Day	Therapy
1, 8, 15, 43, and 50	Vincristine 1.5 mg/m^2 IV. (Maximum dose 2 mg)
1-7; 15-21	Dexamethasone 5 mg/m^2 PO or IV BID
1, 8, and 15	Doxorubicin 25 mg/m^2 IV
4 (or Day 5 or Day 6), 43	Calaspargase pegol (dose per Table (6.1) 1)
29	Cyclophosphamide 1000 mg/m^2 IV on Day 29
29-32, 36-39	Cytarabine 75 mg/m^2 IV or SC
29-42	6-Thioguanine 60mg/m^2 orally daily
1, 29, and 36	Methotrexate 15 mg IT
1, 8 and 29, 36	Rituximab 375 mg/m^2 IV (for CD20+ patients only)

BID = twice daily; IT = intrathecal; IV = intravenous; SC = subcutaneous

Begin Delayed Intensification phase within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study Principal Investigator.

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy on Days 1 and 29 of this course. All therapy should be interrupted for patients with severe infections and should be resumed at the same point when the signs of infection have abated. Hold all Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. Otherwise, therapy should not be interrupted for simple myelosuppression.

Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 8, 15, 43, and 50. Voriconazole and posaconazole should be used with caution with vincristine.

Dexamethasone 5 mg/m^2 PO or IV BID on Days 1 – 7 and 15 – 21. Round to nearest 1 to 2 mg dose.

Doxorubicin 25 mg/m^2/day IV on Days 1, 8, and 15.

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Calaspargase pegol 1500 – 1750 U/m^2 IV (Age 22 to 39: 1750 U/m^2; Age 40 to < 55: 1500 U/m^2) on Day 4 (**OR Day 5 OR Day 6) AND Day 43**. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25 to 50 mg diphenhydramine (or equivalent) 30 to 60 minutes prior to calaspargase pegol. Calaspargase pegol will be administered as a 2-hour infusion. Detailed instructions for calaspargase pegol administration are provided in the Pharmacy Manual.

The calaspargase pegol dose is calculated according to BSA. The BSA will be calculated by using the DuBois formula (Du Bois et al, 1989) (all BSA calculations are rounded to 2 decimal places) (Stewart et al, 2016). Dose capping at 1 vial is not permitted.

Cyclophosphamide 1000 mg/m^2 IV on Day 29. It is recommended to reduce urine specific gravity to ≤ 1.015 prior to administering. Give IV fluids to maintain urine output. May use furosemide 0.25 – 0.5 mg/kg/dose IV for urine output < 3 mL/kg/hour after cyclophosphamide administration.

Cytarabine 75 mg/m^2/day IV or SC on Days 29 – 32 and 36 – 39.

Thioguanine 60 mg/m^2/day PO on Days 29 – 42. Give thioguanine at least 1 hour after evening meal. 6TG is not to be taken with milk or citrus products. Adjust dose using 40 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close as possible to 420 mg/m^2. See Appendix 4 for details. Do not escalate dose based on blood counts during this course.

IT-Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) total dose on Days 1, 29, and 36. Patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy to enhance drug delivery to the head. Send CSF for cell count and cytospin exam.

Rituximab (for CD20+ patients only, as defined in Section 6.2.1.2): 375 mg/m^2 IV on Days 1 and 8 and Days 29 and 36. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent).

Every effort should be made to administer all chemotherapy agents on the day specified in the protocol. However, a window of ± 2 days will allow for weekends, holidays, and any developments in the patient's medical condition that preclude administration on the day specified. The reason for using the window should be captured in the source documents.

Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

6.4.7 Maintenance Therapy

It is recommended that Maintenance therapy be based on CALGB 10403 treatment regimen as described below. Maintenance phase may commence prior to End-of-Treatment visit which is to occur 1 year after the initial dose of calaspargase pegol in Remission Induction phase. All protocol-specified study visits and evaluations will take place within 30 days after the last administration of calaspargase pegol at Day 43 in Delayed Intensification phase. No further study-specific visits will occur during the maintenance phase until the End-of-Treatment (EOT) visit at 1 year, however, serious adverse events related to the research and any concomitant treatments administered should be collected until the EOT visit. After the EOT visit, only survival data will be collected via long-term follow-up. Bone marrow examinations and other

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disease evaluations will be done at the discretion of the investigator. CNS3 patients who achieve a CR may receive concurrent cranial radiation at the discretion of the investigator and per institutional standards. Maintenance therapy (12-week courses/84-day cycles) should begin within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts do not recover within 4 weeks, then contact the study's Principal Investigator. Only mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Appendix 5.

Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 29, and 57. Voriconazole and posaconazole may be used with caution, concomitantly with vincristine.

Dexamethasone 3 mg/m^2 PO or IV BID every 4 weeks **on Days 1 – 5, 29 – 33, and 57 – 61**. Round to the nearest 1 to 2 mg dose.

Mercaptopurine 75 mg/m^2/day PO on Days 1 – 84. 6-MP is to be taken at least one hour after evening meal and should not be taken with milk or citrus products. Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close as possible to 525 mg/m^2/week. See Appendix 4, subsection Mercaptopurine Dosing guidelines. In case of myelosuppression, see Appendix 5.

IT-Methotrexate 15 mg total dose IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Day 1. **IT methotrexate also is given on Day 29 of the first 4 courses of maintenance therapy.** Patients should remain in a horizontal position for at least 30 minutes following the administration of intrathecal chemotherapy to enhance drug delivery to the head. Send CSF for cell count and cytospin exam.

PO-Methotrexate 20 mg/m^2 PO weekly (on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78). Round to nearest 2.5 mg dose. PO methotrexate is held on Day 29 of the first 4 courses of maintenance therapy (when IT Methotrexate is given). See Appendix 5 for dose escalation instructions. If a patient is receiving prophylaxis with cotrimoxazole (sulfamethoxazole/trimethoprim), do not give on the same day as methotrexate administration.

Repeat 12-week Maintenance Therapy courses until total duration of therapy is 2 years from the start of Interim Maintenance for female patients and 3 years from the start of Interim Maintenance for male patients, unless that falls during the 5-day course of steroid, then finish the course of steroids and stop treatment.

Investigator discretion is advised if IT administration is not possible due to a medical condition that prevents performing a lumbar puncture. Reason for delay or omission will be captured in the source documents.

For ANC ≥ 1500/µL on 3 complete blood counts (CBCs) done over 6 weeks or 2 successive monthly CBC(s), first increase the dose of either PO MTX or 6-MP by 25%. Then increase the dose of the other drug by 25%. If there is no fall in ANC after both PO MTX and 6-MP have been increased once, consider noncompliance as a possibility. Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2 to 4 hours later. This will document whether poor absorption contributes to lack of response and may facilitate discussions about noncompliance. **If oral MTX dose is escalated to 40 mg/m^2, contact the Principal Investigator before further escalation.**

6.5 Investigational Medicinal Product Dispensing

Please refer to Section 4.3.2.

6.6 Previous and Concomitant Treatments

6.6.1 Calaspargase pegol

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).
- Methotrexate, vincristine, cytarabine (these agents may increase the action or toxicity of asparaginases and should be administered consistent with the information provided in Appendix 4 and Appendix 5).

Since there is a potential for an indirect interaction between calaspargase pegol and oral contraceptives, the concomitant use of calaspargase pegol and oral contraceptives is not recommended. Another, non-oral contraceptive method should be used in women of childbearing potential.

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 e-CRF.

6.6.2 Backbone Therapies

Because lists of interactions are constantly changing, please consult and review the product information for the backbone regimen (NIMPs) or the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, individual product labeling, or a local institution's pharmacist.

6.6.3 Ancillary Treatments and Supportive Care

Guidelines for the use of permitted concomitant treatments, ancillary therapy and supportive care are provided in Table (6.6.3) 1. Institutional guidelines and Investigator discretion may be applied to supportive care and concomitant treatment, except for prohibited treatments. The study Principal Investigator may be consulted as necessary.

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Table (6.6.3) 1 - Instructions Regarding Ancillary Treatments and Supportive Care

Treatment or Supportive Care	Instructions
Non-protocol treatment for ALL	Other agents for treatment for the primary neoplasm or that would impact interpretation of the primary endpoint data are prohibited
Supportive care	Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the enrollment until the End-of-Treatment visit (or 30 days after the final dose if early discontinuation) will be recorded in the medical records
Hormones	Hormones that could be considered as treatment for the primary neoplasm or might impact the primary endpoint are prohibited except for: - steroids given for adrenal failure - hormones administered for non-disease-related conditions (*e.g.*, insulin for diabetes)
Antiemetics	Allowed at the discretion of the Investigator, with the exception of steroids above
Antidiarrheals	Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide. Patients with severe diarrhea should be assessed for IV hydration and correction of electrolyte imbalances.
Radiotherapy	Palliative radiation therapy will be administered per institutional protocol and Investigator judgment. It is recommended that it may not be administered (except for whole-brain irradiation given for documented CNS3 disease in CR or clinical evidence of testicular disease at diagnosis and persisting at the end of induction therapy). Do not hold protocol chemotherapy during CNS irradiation. Irradiate a symptomatic lesion, or one that may produce disability (*e.g.*, unstable femur) prior to study initiation, provided other measurable disease is present. Patients who require radiation therapy (except for whole-brain irradiation given for documented CNS3 disease in CR or clinical evidence of testicular disease at diagnosis and persisting at the end of induction therapy) during protocol treatment will be evaluated for potential treatment discontinuation due to disease progression. Investigator discretion will be applied, and study Principal Investigator may be consulted.
Blood Products and Growth factors	Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow the published ASCO guidelines (ASCO Practice Guideline)
Filgrastim (G-CSF), tbo-filgrastim, and sargramostim (GM-CSF)	Use of these agents is discouraged, and may not be used to avoid dose reductions, delays or to allow for dose escalations. If they are used, they must be obtained from commercial sources. For the treatment of febrile neutropenia, the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome), or fungal infection, as per the ASCO guidelines (ASCO Practice Guideline). Investigators should therefore use their own discretion in using the CSFs in this setting and consult the study Principal Investigator if needed. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
Erythropoietin Darbepoetin	Prohibited
Agents to treat hypersensitivity and/or infusion reactions	Follow institutional standards

Treatment or Supportive Care	Instructions
CYP3A4 Inhibitors	Chronic concomitant treatment with strong inhibitors of CYP3A4 should be used with caution during protocol therapy on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4: - Indinavir - Clarithromycin - Ketoconazole - Voriconazole - Posaconazole Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist
CYP3A4 Inducers	Chronic concomitant treatment with strong inducers of CYP3A4 should be used with caution during protocol therapy on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4: - Rifampin - Carbamazepine Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist

ASCO = American Society of Clinical Oncology; CNS = central nervous system; CR = complete remission; CSF = cerebrospinal fluid;
FDA = Food and Drug Administration; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor

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A list of prohibited and unauthorized treatments by drug class is provided in the eCRF guide and in Table (6.6.3) 2. Detailed drug information for the backbone chemotherapy agents, including adverse event profile and drug interactions, is provided in Appendix 4. Dose and treatment modification instructions for the backbone products are included in Appendix 5.

Table (6.6.3) 2 - Prohibited and Unauthorized Treatments

Prohibited Medications:	• Other agents for treatment for the primary neoplasm or that would impact interpretation of the primary endpoint data are prohibited: ▪ Hormones that could be considered as treatment for the primary neoplasm or might impact the primary endpoint are prohibited except for: - Steroids given for adrenal failure. - Hormones administered for non-disease-related conditions (*e.g.*, insulin for diabetes). • Erythropoietin, darbepoetin. • Cryoprecipitate replacement contains prothrombotic factors, which may promote thrombosis. Its administration was reported to be associated with a higher rate of thrombosis (Orvain et al., 2020). Despite the high frequency of hypofibrinogenemia in adults with ALL receiving asparaginase therapy, it has not been typically associated with an increased risk of major bleeding (Aldos et al., 2016). Use of prophylactic cryoprecipitate replacement for hypofibrinogenemia is not permitted unless patients have active bleeding, are at high-risk of bleeding while on full-dose anticoagulation, or undergoing an invasive procedure (Burke et al, 2020; Douer et al., 2021).
Use Discouraged:	Filgrastim (G-CSF), tbo-filgrastim, and sargramostim(GM-CSF): may not be used to avoid dose reductions, delays or to allow for dose escalations. If they are used, they must be obtained from commercial sources.
Use with Caution During Treatment:	• Live vaccines • Coumarin/warfarin and heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory medicines (*e.g.* ibuprofen, naproxen). • Methotrexate, vincristine, cytarabine (these agents may increase the action or toxicity of asparaginases and should be administered consistent with the information provided in Appendix 4 and Appendix 5) • Strong CYP3A4 Inhibitors: Chronic concomitant treatment with strong inhibitors of CYP3A4 should be used with caution during protocol therapy on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4: indinavir, clarithromycin, ketoconazole, voriconazole, posaconazole. • Strong CYP3A4 Inducers: Chronic concomitant treatment with strong inducers of CYP3A4 should be used with caution during protocol therapy on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4: rifampin, carbamazepine • Since there is a potential for an indirect interaction between calaspargase pegol and oral contraceptives, the concomitant use of calaspargase pegol and oral contraceptives is not recommended. Another non-oral contraceptive method should be used in women of childbearing potential.

The patient must be told to notify the investigational site about any new medication 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 e-CRF.

6.7 Investigational Medicinal Product Compliance

The number of injectable vials dispensed and the infused volume are to be counted by the Investigator or a designated person from his/her team and recorded in the e-CRF and RTSM, or an equivalent document.

The compliance will be assessed from the method described above.

6.8 Discontinuation of the Investigational Medicinal Product

After the discontinuation of the IMP, patient's treatment is left to the physician's discretion.

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7 ASSESSMENT OF EFFICACY

Responses, including morphologic CR and morphologic CR rate with incomplete blood count recovery (CRi), and negative MRD rate (MRD < 10^{-4}) will be defined according to the NCCN ALL guidelines (Clinical Practice Guidelines).

7.1 Efficacy Measurements

An objective response will be defined as: (1) a morphologic CR (Clinical Practice Guidelines) (2) a CR with CRi or a molecular response defined as a MRD below a sensitivity threshold of < 10^{-4} (0.01%) (Bruggemann et al, 2008) according to the assessments of patient samples described above.

Disease free survival, event free survival, and OS will be assessed according to the analyses plan described in Section 10.1.2.3.

7.2 Methods and Measurement Times

The evaluation of the tumor load will be performed on bone marrow aspirate (BMA), and CBC with evaluation of CNS involvement and extramedullary disease per NCCN and institutional guidelines (Clinical Practice Guidelines), as clinically indicated.

7.2.1 Evaluation of Central Nervous System Involvement

CNS involvement will be assessed via CSF cell count and cytospin exam at scheduled IT administrations.

CNS remission is defined as achievement of CNS-1 status in a subject with CNS-2 or CNS-3 status at diagnosis. CNS relapse is defined as new development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation (Clinical Practice Guidelines).

7.2.2 Evaluation of Extramedullary Disease

Extramedullary disease may be evaluated by contrast-enhanced computerized tomography (CT; neck, chest, abdominal, or pelvic) and positron emission tomography (PET)/CT. The response criteria per NCCN guidelines is presented in Table (7.2.2) 1. Extramedullary disease will be assessed as clinically indicated according to NCCN criteria 2023 (Clinical Practice Guidelines) and per the institutional guidelines.

Table (7.2.2) 1 - Response Criteria for Lymphomatous Extramedullary Disease

Category	Description
CR	Complete
PR	>50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the lymphomatous enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
PD	>25% increase in the SPD of the lymphomatous enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
NR	Failure to qualify for PR or PD.
Relapse	Recurrence of lymphomatous enlargement after achieving CR. At least one of the previously observed lesions is positive on post-treatment PET for subjects who had a positive result on previous PET. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

CR = complete remission; CT = computerized tomography; NR = no response; PET = positron emission tomography; SPD = greatest perpendicular diameters

7.2.3 Minimal Residual Disease

BMA will be obtained during the screening phase and at specified evaluation time points for MRD status evaluation.

MRD status and clinical decision-making will be determined using each site's local laboratory results; these results will be collected in the clinical database. MRD assessment will also be performed centrally to support regulatory approval and the secondary efficacy endpoint.

For central MRD analysis, 2 mL of first aspirate BMA will be collected at each specified time point. Local assessment of MRD will be performed according to institutional practices. As local BMA and MRD laboratory results will be used for patient management and clinical decision-making, it is recommended that, whenever possible, local BMA should be collected at the same time points with central laboratory samples.

Only in case insufficient BMA is collected at the pre-treatment time point, a 4 mL sample of peripheral blood will be collected, provided there are sufficient numbers of circulating lymphoblasts (at least 1000/µL).

Additional details and sample collection instructions are provided in the laboratory manual.

7.2.3.1 Bone Marrow Aspirate Collection Time Points

The tumor load will be evaluated all along the study up to the end-of-treatment visit (Note: A ± 2-day window for BMA sample collection for MRD central assessment is permitted as long as the patient has adequate blood count recovery after aplasia):

- Pre-treatment.
- During Remission Induction phase at Day 29 (± 2 days).
- During Remission Consolidation phase at Day 56 (± 2 days).
- During Delayed Intensification phase at Day 50 (± 2 days).
- In case of premature withdrawal (at the Investigator's discretion).
- At any time in case of suspicion of disease relapse up to the Investigator's judgement.
- At the End-of-Treatment visit (at the investigator's discretion).

7.2.3.2 Bone Marrow and Minimal Residual Disease Status at the End of Remission Induction

A bone marrow aspirate specimen must be obtained for all patients on Day 29 to assess induction response and minimal residual status. M status will be evaluated according to the definition provided in Table (7.2.3.2) 1. Note that a bone biopsy is not needed unless it's a part of the site's standard practice. If a biopsy is obtained, the results should be entered onto the eCRF.

Table (7.2.3.2) 1 - Bone Marrow M Status Definitions

Rating	Blast Cells (%)[1]
M0	0 – 5.0
M1	0 – 5.0
M2	5.1 – 25.0
M3	> 25.0 – 50.0
M4	> 50.0

1. *The term "blast cell" includes any cell that cannot be classified as a more mature normal element, and includes "leukemic cells," pathologic lymphocytes, and stem cells.*

Patients with bone marrow M status: M3 or M4 (greater than 25% lymphoblasts) will not be eligible for the Remission Consolidation phase and will have to discontinue the study. Another treatment option will be proposed by the Investigator. Patients with M0-M2 will continue to Remission Consolidation phase.

7.2.3.3 Bone Marrow and Minimal Residual Disease Status and the End of Remission Consolidation

A bone marrow aspirate specimen will be obtained for all patients at Day 56 Remission Consolidation phase. If at the end of the Remission Consolidation phase there is evidence of MRD as demonstrated by MRD > 10^{-4} detectable leukemia cells in the bone marrow, any further treatment will be based on the Investigator discretion. If hematopoietic stem cell transplantation (HSCT) or any other non-protocol treatments are indicated, the patient will be discontinued from the study. Note that a bone biopsy is not needed unless it is a part of a site's standard practice. If a biopsy is obtained, the results should be entered onto the eCRF.

7.2.4 Local Laboratory Parameters

The local laboratory parameters to be collected in the eCRF are:
- Cytogenetics data at baseline, time of first CR and at relapse (per investigator's discretion).
- Fluorescence in situ hybridization (FISH) data at baseline, time of first CR and at relapse (per investigator's discretion).

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8 ASSESSMENT OF SAFETY

All AEs 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

The safety measurements to be performed during the study are indicated in Section 4.1.2.
Safety assessment of calaspargase pegol will include AE assessments, physical examination, ECOG PS.

- Vital signs (*i.e.,* blood pressure, weight, height, heart rate, body temperature).
- ECG measurements.
- Laboratory evaluations: hematology, biochemistry and coagulation parameters.

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

Any abnormality detected during safety assessments from the time of the informed consent until the End-of-Treatment or Early Discontinuation visit must be reported on the e-CRF page at each study visit.

8.2 Methods and Measurement Times

Relevant Medical History
Relevant medical history will be reported to identify any medical condition which could preclude the patient's participation:

- 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 Sign Measurements:

- Pregnancy tests will only be performed for women of childbearing potential (Section 5.5).
- Complete clinical examination, height and weight measurement and ECOG assessment will be performed. Magnetic resonance imaging (MRI)/PET/CT scans should be performed if indicated.
- 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.
- Chest X-ray.

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.

At screening the initial WBC count and differential should be the first WBC count prior to receiving any steroid therapy; the initial platelet count is prior to any transfusion, and the initial hemoglobin level is prior to IV fluids or transfusions.

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If several laboratory results are available from before the first study drug administration, the results from the laboratory evaluations performed just before the first study drug administration may be considered as the baseline value and used to determine the baseline grade.

The laboratory parameters to be collected are described in Table (8.2) 1.

Table (8.2) 1 - Local Clinical Laboratory Parameter Collection Plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, RBCs, WBCs, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts in absolute value and in %)
Biochemistry	Total protein, Albumin, ALP, ALT, AST, GGT, Ammonia, Bicarbonates, 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
Urinary analysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, Protein) If the dipstick test is at least 2+ on 1 or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s)
Blood coagulation	PT-INR, fibrinogen, protein S activity, aPTT, D-dimer, and ATIII (see Section 8.6.3 for coagulopathy monitoring)
Hepatitis B and C	Hepatitis B surface antigen and Hepatitis C antibody
Pregnancy Test	Pregnancy testing is mandatory at inclusion (serum), before each calaspargase pegol administration (urine) and at withdrawal visit (urine) for women of childbearing potential

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = Antithrombin III; BUN = blood urea nitrogen; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PT-INR = prothrombin time and international normalized ratio; RBC = red blood cell; WBC = white blood cells

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.

ECGs will be assessed during screening phase and the End-of-Treatment or Early Discontinuation visit.

Left-Ventricular Ejection Fraction (LVEF) assessment will be performed through echocardiography or MUGA scan during screening, and at the End-of-Treatment or Early Discontinuation visit.

The same technique, either ECHO or MUGA, should be used throughout the study for a given patient.

8.2.1 Screening Period and Inclusion

Prior to inclusion, the clinical assessment will include:

- Medical and surgical history.
- Previous and concomitant treatments.
- Physical examination (within 7 days before the inclusion): a complete physical examination (per institutional standards), including vital signs (temperature, HR, BP), weight, height [at Screening only, for calculation of BSA], and ECOG PS.
- Laboratory tests:
  - Blood hematology with differential (within 7 days before inclusion): hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
    - Coagulopathy tests (within 7 days before inclusion): prothrombin time - International Normalized Ratio (INR), fibrinogen, aPTT, D-dimer, protein S activity, and ATIII.
    - Biochemistry tests (within 7 days before inclusion):
      - Serum creatinine, creatinine clearance, blood urea nitrogen (BUN), electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium, phosphate), ammonia, total protein, albumin.
      - Liver function tests: AST, ALT, ALP, gamma glutamyl transferase (GGT), direct bilirubin and total bilirubin.
      - Pancreatic enzymes (amylase/lipase) and glucose.
      - Triglycerides, total cholesterol, LDL, HDL.
      - lactate dehydrogenase (LDH).
      - Uric acid.
- Urinary analysis (within 7 days before inclusion): macroscopic panel (dipstick) (blood, glucose, ketones, protein):
  - If the dipstick test is at least 2+ on 1 or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s).
- Hepatitis B (HBs antigen) and Hepatitis C (HCV antibody) testing at screening only; within 7 days of inclusion.
- Pregnancy tests for women of childbearing potential (serum) within 7 days before inclusion.
- Cardiac function assessment performed by echocardiography or MUGA scan.
- ECG.
- Chest X-ray.

8.2.2 During the Treatment Period

Remission Induction Phase

- Concomitant treatments: throughout the Remission Induction phase.
- AEs: throughout the Remission Induction phase.
- Physical examination: (per institutional standards): weekly or more frequently if clinically indicated, including vital signs (temperature, HR, BP), weight, BSA, and ECOG PS at Day 4 predose.

- Laboratory tests:
  - Blood hematology with differential:
    - Parameters: hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
    - Time points (weekly assessment or more frequently if clinically indicated):
      - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), and Day 29 (+/-3 days).
- Coagulopathy tests:
  - Parameters: PT- INR, fibrinogen, aPTT, D-dimer, and ATIII.
  - Time points: (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
    - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), and Day 29 (+/-3 days).
- Biochemistry tests:
  - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin:
    - Time points (weekly assessment or more frequently if clinically indicated).
    - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), and Day 29 (+/-3 days).
- Liver function tests:
  - Parameters: AST, ALT, ALP, direct bilirubin and total bilirubin.
  - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
    - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), and Day 29 (+/-3 days).
- Pancreatic enzymes (amylase/lipase) and Glucose:
  - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
    - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), and Day 29 (+/-3 days).
- Triglycerides:
  - Time points: Day 4 pre-dose.
- LDH:
  - Time points Day 4 pre-dose (then weekly until the levels are within the normal range).
- Phosphate and Uric Acid:
  - Time points Day 4 pre-dose (then weekly until the levels are within the normal range).
- Pregnancy tests for women of childbearing potential (urine): Day 4 pre-dose.

Remission Consolidation Phase

- Concomitant treatments: all along the Remission Consolidation phase.
- AE: all along the Remission Consolidation phase.
- Physical examination: (per institutional standards): weekly or more frequently if clinically indicated, including vital signs (temperature, HR, BP), weight, BSA, and ECOG PS at Day 15 predose and Day 43 predose.

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- Laboratory tests:
  - Blood hematology with differential:
    - Parameters: hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
    - Time points (weekly assessment or more frequently if clinically indicated):
      - For weekly assessment: Day 8 (+/-3 days), Day 15 pre-dose, Day 22 (+/-3 days), Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), and Day 57 (+/-3 days).
- Coagulopathy tests:
  - Parameters: PT-INR, fibrinogen, aPTT, D-dimer, and ATIII.
  - Time points: (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
    - For weekly assessment: Day 8 (+/-3 days), Day 15 pre-dose, Day 22 (+/-3 days), Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), and Day 57 (+/-3 days).
- Biochemistry tests:
  - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin:
    - Time points (weekly assessment or more frequently if clinically indicated):
      For weekly assessment: Day 8 (+/-3 days), Day 15 pre-dose, Day 22 (+/-3 days), Day 29(+/-3 days), Day 36 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), and Day 57 (+/-3 days).
  - Liver function tests:
    - Parameters: AST, ALT, ALP, direct bilirubin and total bilirubin.
    - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
      For weekly assessment: Day 8 (+/-3 days), Day 15 pre-dose, Day 22 (+/-3 days), Day 29(+/-3 days), Day 36 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), and Day 57 (+/-3 days).
  - Pancreatic enzymes (amylase/lipase) and Glucose:
    - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
      For weekly assessment: Day 8 (+/-3 days), Day 15 pre-dose, Day 22 (+/-3 days), Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), and Day 57 (+/-3 days).
  - Triglycerides:
    - Time points: Day 15 pre-dose and Day 43 pre-dose.
  - Pregnancy tests for women of childbearing potential (urine): Day 15 pre-dose and Day 43 pre-dose.

Interim Maintenance Phase

- Concomitant treatments: all along the Interim Maintenance phase.
- AE: all along the Interim Maintenance phase.
- Physical examination: (per institutional standards): weekly or more frequently if clinically indicated, including vital signs (temperature, HR, BP), weight, BSA, and ECOG PS at Day 22 pre-dose.

- Laboratory tests:
  - Blood hematology with differential:
    - Parameters: hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
    - Time points (weekly assessment or more frequently if clinically indicated):
      - For weekly assessment: Day 2 (+/-3 days), Day 9 (+/-3 days), Day 16 (+/-3 days), Day 22 pre-dose, Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 (+/-3 days).
  - Coagulopathy tests:
    - Parameters: PT-INR, fibrinogen, aPTT, D-dimer, and ATIII.
    - Time points: (Twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
      - For weekly assessment: Day 2 (+/-3 days), Day 9 (+/-3 days), Day 16 (+/-3 days), Day 22 pre-dose, Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 (+/-3 days).
  - Biochemistry tests:
    - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin:
      - Time points (weekly assessment or more frequently if clinically indicated):
        For weekly assessment: Day 2 (+/-3 days), Day 9 (+/-3 days), Day 16 (+/-3 days), Day 22 pre-dose, Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 (+/-3 days).
    - Liver function tests:
      - Parameters: AST, ALT, ALP, direct bilirubin and total bilirubin.
      - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
        For weekly assessment: Day 2 (+/-3 days), Day 9 (+/-3 days), Day 16 (+/-3 days), Day 22 pre-dose, Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 (+/-3 days).
    - Pancreatic enzymes (amylase/lipase) and Glucose:
      - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
        For weekly assessment: Day 2 (+/-3 days), Day 9 (+/-3 days), Day 16 (+/-3 days), Day 22 pre-dose, Day 29 (+/-3 days), Day 36 (+/-3 days), Day 43 (+/-3 days).
    - Triglycerides:
      - Time points: Day 22 pre-dose.
  - Pregnancy tests for women of childbearing potential (urine): Day 22 pre-dose.

Delayed Intensification Phase

- Concomitant treatments: all along the Delayed Intensification phase.
- AE: all along the Delayed Intensification phase.
- Physical examination: (per institutional standards): weekly or more frequently if clinically indicated, including vital signs (temperature, HR, BP), weight, BSA, and ECOG PS at Day 4 predose and Day 43 predose.
- Laboratory tests:
  - Blood hematology with differential:
    - Parameters: hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
    - Time points (weekly assessment or more frequently if clinically indicated):
      - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), Day 25 (+/-3 days), Day 32 (+/-3 days), Day 39 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), Day 57 (+/-3 days), and Day 64 (+/-3 days).

- Coagulopathy tests:
  - Parameters: PT-INR, fibrinogen, aPTT, D-dimer, and ATIII.
  - Time points: (Twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
    - For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), Day 25 (+/-3 days), Day 32 (+/-3 days), Day 39 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), Day 57 (+/-3 days), and Day 64 (+/-3 days).
- Biochemistry tests:
  - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium), ammonia, total protein, albumin:
    - Time points (weekly assessment or more frequently if clinically indicated):
      For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), Day 25 (+/-3 days), Day 32 (+/-3 days), Day 39 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), Day 57 (+/-3 days), and Day 64 (+/-3 days).
  - Liver function tests:
    - Parameters: AST, ALT, ALP, direct bilirubin and total bilirubin.
    - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
      For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), Day 25 (+/-3 days), Day 32 (+/-3 days), Day 39 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), Day 57 (+/-3 days), and Day 64 (+/-3 days).
  - Pancreatic enzymes (amylase/lipase) and glucose:
    - Time points (twice-weekly (+/-2 days) while hospitalized, then weekly thereafter or more frequently if clinically indicated):
      For weekly assessment: Day 4 pre-dose, Day 11 (+/-3 days), Day 18 (+/-3 days), Day 25 (+/-3 days), Day 32 (+/-3 days), Day 39 (+/-3 days), Day 43 pre-dose, Day 50 (+/-3 days), Day 57 (+/-3 days), and Day 64 (+/-3 days).
  - Triglycerides:
    - Time points: Day 4 pre-dose and Day 43 pre-dose.
- Pregnancy tests for women of childbearing potential (urine): Day 4 pre-dose and Day 43 pre-dose.

8.2.3 End-of-treatment Visit/Early Termination Visit

- Concomitant treatments.
- AE assessment.
- Physical examination.
- Vital signs.
- ECOG PS.
- Laboratory tests including:
  - Blood hematology with differential: hematocrit, hemoglobin, RBCs, WBCs, platelets, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, blasts in absolute value and in %).
  - Coagulopathy tests: PT-INR, fibrinogen, aPTT, D-dimer, and ATIII.
- Biochemistry tests:
  - Serum creatinine, creatinine clearance, BUN, electrolytes (bicarbonates, sodium, potassium, calcium and corrected calcium, phosphate), ammonia, total protein, albumin.
  - Liver function tests: AST, ALT, ALP, GGT, direct bilirubin and total bilirubin.
  - Pancreatic enzymes (amylase/lipase) and glucose.

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  - Triglycerides, total cholesterol, LDL, HDL.
  - LDH.
  - Uric Acid.
- Urinary analysis: macroscopic panel (dipstick) (blood, glucose, ketones, protein).
  - If the dipstick test is at least 2+ on 1 or more parameter(s), quantitative urinary biochemistry tests will be performed on the abnormal parameter(s).
- Pregnancy test (urine) for women of childbearing potential.
- Cardiac function assessment performed by echocardiography or MUGA scan.
- ECGs.

8.2.4 Long-term Survival Follow-up

After the End-of-Treatment visit a telephone call will be done every 3 months for up to 2 years, for a total of 3 years of survival follow-up since the initial calaspargase administration at Remission Induction. Patients who discontinued early, did not switch to an alternative therapy for ALL treatment, and completed their Early Discontinuation/End of Treatment evaluations, will be followed for a total of 3 years after their initial calaspargase dose in the induction phase. Patients who withdrew consent or switched to an alternative therapy for ALL treatment will not be contacted.

The following information will be collected during the telephone contact:
- The participant's survival.
- Disease status.

Information on disease status, relapse and survival will be obtained at the clinical site for evaluation of long-term EFS, DFS and OS.

8.3 Definition of Adverse Events

An AE 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/NIMP 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.* run-in period) are also concerned).

An AE can therefore be:
- Any unfavorable and unintended sign (including an abnormal finding from an additional examination such as laboratory tests, X-rays, ECGs) 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).

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 calaspargase pegol in Remission Induction phase to 30 days after the last dose of calaspargase pegol in the study.

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Of note:
Any hospitalization 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 AE and should not be reported in the e-CRF.

The following procedures, whether planned before the study or not, whether leading to a hospitalization 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, hemodialysis sessions related to a renal insufficiency not aggravated during the study).
- Prophylactic procedures (*e.g.* sterilization, 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 AE 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 hospitalization, but might jeopardize the participant or might require intervention to prevent one of these outcomes (for example: edema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalization, 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 for the cohort in the study protocol, independent of the occurrence of any AE.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol.

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8.6 Definition of Adverse Event of Special Interest

An AESI 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 would be needed. It may be a serious or non-serious AE that may require further investigation in order to characterize and understand.

For calaspargase pegol, AESI include:
- Grade ≥ 3 ALT/AST increase or Grade ≥ 3 hyperbilirubinemia (Section 8.6.1).
- Grade ≥ 3 pancreatitis (Section 8.6.2).
- Grade ≥ 3 hemorrhage and all thromboembolic events regardless of the grade, excluding catheter-related events (Section 8.6.3.1 and Section 8.6.3.2).
- Grade ≥ 3 hypersensitivity/infusion reactions per CTCAE v5.0 (Section 8.6.4).

AESI monitoring is to be performed as described in Sections 8.6.1, 8.6.2, 8.6.3, and 8.6.4. Those events will be immediately reported even if the event is considered non-serious according to the usual seriousness criteria. A specific documentation will be required.

Safety boundaries that evaluate the rate of AESIs (hyperbilirubinemia, thrombosis, pancreatitis, and hypersensitivity) are provided. Once a safety boundary is reached, patient enrollment ~~in the~~ will be suspended until all available safety data are evaluated by the DSMB and a decision is made whether to permanently stop further enrollment. Additionally, once a safety boundary is reached, newly-enrolled patients who have not yet been administered the study drug will have the dose withheld. These safety boundaries defined in Table (8.6) 1.

Table (8.6) 1 – Adverse Events of Special Interest: Safety Boundaries and Pausing Criteria

AESI Category	Number of Patients Enrolled in Part 2	Pause Enrolling When Number of Patients with AESI is Greater than or Equal to
Grade ≥3 Hyperbilirubinemia (historical estimate = 27.7%) (Section 8.6.1)	≤ 20	9
	21 - 40	16
	41 - 60	22
	61 - 80	28
	81 - 100	34
Grade ≥3 Pancreatitis (historical estimate = 7.5%) (Section 8.6.2)	≤ 20	4
	21 - 40	6
	41 - 60	8
	61 - 80	10
	81 - 100	12
Any Grade Thrombosis (historical estimate = 18.4%) (Section 8.6.3.2)	≤ 20	7
	21 - 40	12
	41 - 60	16
	61 - 80	20
	81 - 100	24
Grade ≥3 Hypersensitivity (historical estimate = 16.6%) (Section 8.6.4)	≤ 20	7
	21 - 40	11
	41 - 60	15
	61 - 80	19
	81 - 100	22

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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, GGT, direct bilirubin and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing as follows:

- For direct bilirubin increase ≥ 3.1 mg/dL, hold calaspargase and monitor the patient weekly including Liver Function Tests (LFTs): albumin, ALT, AST, GGT, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 x ULN), or more frequently if clinically indicated, until values have resolved to baseline or stabilized over 4 weeks with direct bilirubin < 2.0 mg/dL.
- Calaspargase pegol will be permanently discontinued if direct bilirubin is ≥ 3.1 mg/dL, does not return to < 2 mg/dL and requires a ≥ 28-day delay in the start of the next scheduled cycle of chemotherapy
- For AST or ALT increase to Grade 3 (> 5.0 – 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal) hold calaspargase and monitor the patient weekly including LFTs [albumin, ALT, AST, GGT, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 x ULN) or more frequently if clinically indicated, until AST or ALT returns to ≤ Grade 2.
- Calaspargase pegol will be permanently discontinued if AST and/or ALT is Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal), does not return to ≤ Grade 2 and there is a ≥ 28-day delay in the start of the next scheduled cycle of chemotherapy.

Refer to Section 8.11 Management of Treatment Dose Adaptations due to Toxicities for detailed recommendations on withholding or permanently discontinuing calaspargase pegol for hepatic toxicities.

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; nonalcoholic steatohepatitis; and biliary tract disease.
  - Considering gastroenterology or hepatologist consultations.

For details on toxicity management please refer to Section 8.11.

8.6.2 Pancreatitis Monitoring

Patients should not use calaspargase pegol if they have a history of clinical pancreatitis.

Patients should be informed of the symptoms of pancreatitis, such as persistent abdominal pain and requested to notify the Investigator if they occur.

Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation also in case of significant hypertriglyceridemia. A CT scan or other imaging test to assess the pancreas, liver, and gallbladder may be considered within 1 week of

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the first occurrence of any Grade ≥ 3 amylase and/or lipase increase per the Investigator's decision or as clinically indicated.

If clinical pancreatitis is suspected, treatment with calaspargase pegol should be suspended. In case of clinical pancreatitis Grade ≥ 3, the patient should never take calaspargase pegol.

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

For details on toxicity management please refer to Section 8.11.

8.6.3 Coagulopathy Monitoring

Coagulopathy (increased prothrombin time [PT], increased activated partial prothrombin time [PTT], and hypofibrinogenemia), which can lead to hemorrhage or thromboembolic events, has been reported in clinical trials with calaspargase pegol.

Antithrombin (AT) functional levels should be checked and repleted as needed according to institutional standards. If no institutional practices are established, the following guidelines may be followed for repletion as needed for a goal AT nadir >50%. Optimal antithrombin target range is in the 80-120%.

- AT units = [(desired AT% - baseline AT %) x weight (kg)] / 1.4
- Please note: Heparin efficacy requires that the AT functional level is adequate. AT replacement is often required during low-molecular-weight heparin (LMWH) therapy while on asparaginase. Replete as needed for those patients with subtherapeutic anti-Xa levels

If AT levels are followed and repleted for a selected goal nadir, check AT levels **twice weekly and replete as needed.** Once a trend in AT levels is established at optimal levels, the schedule for checking AT may be altered and be resumed as routinely indicated according to schedule of assessments (Table (4.1.2.1.1) 1, Table (4.1.2.2) 1, Table (4.1.2.3) 1, Table (4.1.2.4) 1, and Table (4.1.2.5) 1).

8.6.3.1 Hemorrhage

Coagulation parameters should be monitored at baseline and periodically during and after treatment, particularly when other medicinal products with 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.

Patients should notify the Investigator if they suffer from a bleeding disorder and if they are also receiving any drugs with anticoagulant effects.

Patients should notify the Investigator immediately if they have severe bleeding or bruising. If hemorrhage Grade ≤ 2, evaluate for coagulopathy and consider clotting factor replacement as needed.

For details on toxicity management please refer to Section 8.11.

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8.6.3.2 Thromboembolic Events

Coagulation parameters will be monitored regularly (Section 8.6.3), especially when other medications with pro-/anti-coagulant effects are given concomitantly.

Patients should notify the Investigator if they have ever had serious blood clots. They should also notify the Investigator if they are receiving other medications with pro-/anti-coagulant effects.

Patients should notify the Investigator immediately if they have any blood clots.

For details on toxicity management please refer to Section 8.11.

8.6.4 Hypersensitivity Monitoring

Hypersensitivity reactions to calaspargase pegol, including life-threatening anaphylaxis, can occur during therapy. Other hypersensitivity reactions can include angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnea, pruritus, and rash.

Patients' vital signs (BP, HR, temperature) during each infusion of calaspargase pegol should be monitored for 1 hour after the end of the calaspargase pegol infusion. Resuscitation equipment and other appropriate means for the treatment of anaphylaxis should be available (epinephrine, oxygen, IV steroids, antihistamines etc.). Calaspargase pegol infusion should be interrupted in patients with Grade 2 or higher infusion reaction or hypersensitivity. Reactions of Grade 2 severity require dose interruption with treatment of the symptoms; the dose can be resumed at 50% infusion rate upon resolution of the symptoms. Patients with Grade ≥ 3 reactions will have their dose permanently discontinued.

Details on calaspargase pegol infusion management are provided in Section 8.11.

8.7 Recording of Adverse Events

The Sponsor must be **notified immediately** (*i.e.*, without delay and **within 24 hours** at the latest) if an event is:

- Serious.
- An AESI.
- An overdose of the IMP/NIMP even if asymptomatic.
- Any intake of the IMP/NIMP by a person around the participant.
- A pregnancy of the participant.
- A pregnancy of the partner of a male participant must also be reported immediately to the Sponsor.

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 **intensity** of the event as well as the **cause-effect relationship** between an AE and the research (IMP/NIMP or study procedure). This evaluation must be assessed by the Investigator and reported in the AE form. In addition, the Sponsor will be responsible for the evaluation the **expectedness** of the event (see Section 8.9.3).

The seriousness should be evaluated according to international guidance (see definition in 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 NCI-CTCAE (v5.0) on a 5-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 activities of daily living (ADL).[4]
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[5]
- 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:
- AE related to IMP.
- AE related to study protocol, *i.e.* related to:
  - A procedure scheduled in the study protocol (*i.e.* exercise test, MRI, etc.…).
  - A change or withdrawal of previous/concomitant treatment related to the condition 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 test drug…), 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".

If in the Investigator's opinion there is a causal relationship with the NIMP, the AE must be considered as related to study protocol.

8.9 Reporting Procedures

8.9.1 Timeframe for Adverse Event Reporting

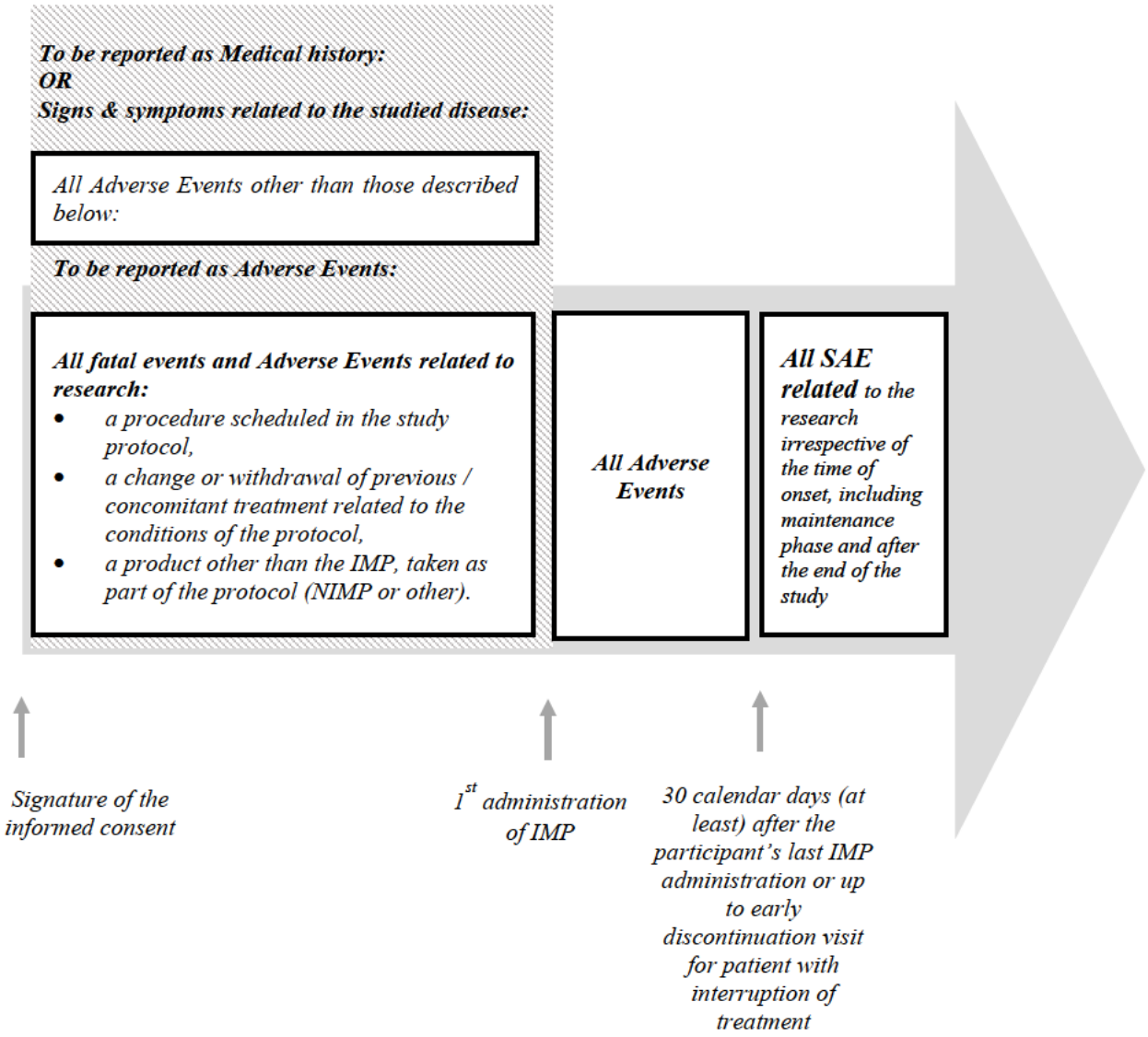
Any event meeting the above-mentioned definitions (see Sections 8.3 to 8.8) must be reported to the Sponsor on an AE form if it occurred:
- Before the first administration of IMP, for fatal events and events related to the research (NIMP or study procedure).
- At any time after the first administration of the **IMP:**
  - Up to 30 calendar days after the participant's last study visit IMP administration for all adverse events. Of note, during the study, some IMP administration intervals are > 30 days, in this case, all adverse events must be reported until next IMP dosing.
  - Up to last study visit (early discontinuation visit) if the IMP was discontinued during the treatment phase, but the early discontinuation visit occurred after 30 days subsequent to the last administration of IMP. In this case, all AEs should be collected up to the early discontinuation visit, even if it occurs > 30 days post last-IMP.

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

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Of note, serious AE related to the research (IMP, NIMP or experimental procedure) should be continued to be collected after the standard AE collection period (30 days after the last IMP administration or after last study visit) irrespective of the time of onset, including maintenance phase and after the end of the study.

Events occurring between the signature of the informed consent and the first administration of the IMP/NIMP 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 or symptoms related to the studied disease** in the dedicated form of the e-CRF. Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on AE form.



8.9.2 Responsibilities of the Investigator

For any AE 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 Serious AE, an AESI, an overdose, an intake by a person around the participant or a pregnancy, 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 IRB/IEC, in accordance with local regulations.

Moreover, the Investigator must report to the Sponsor and/or to the IRB/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 test drug or that would be sufficient to consider changes in the test drug 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. He/She should provide anonymized copies of relevant source documents and additional documents, if requested by the sponsor.

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 AE already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" page previously created for the event.

If the AE 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 the "Adverse Event" page previously created for the event

If the follow-up of the participant is not done by the Investigator him/herself (hospitalization, 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 Investigational- and Non-investigational Medicinal Product by a Person around The Participant)

Pregnancy

If a female participant in the study becomes pregnant, the Investigator must:
- Stop immediately the test drug (since pregnancy is a non-inclusion/exclusion criterion).
- Report it on an "Adverse Event" page as well as on the specific paper pregnancy form (1st page) to be notified immediately.

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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 Investigational Medicinal Product or Non-investigational Medicinal Product
In case of overdose, the Investigator should report it on an "Adverse Event" page to be notified immediately.

Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
- Dose details (number of units, duration, etc.) 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.

Intake of Investigational Medicinal Product or Non-investigational Medicinal Product 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 AE.
- On the other hand, for the following diseases, any episode will be documented as an AE.
- 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.

Moreover, specific additional information will be collected/specific management will be ensured for the events reported in Section 8.6.

8.9.2.5 Procedure for recording Adverse events with immediate notification

In case of an event (a Serious AE, an AESI, an overdose, an intake by a person around the participant or a pregnancy), 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 EDC, an e-mail will be immediately and automatically sent to the Sponsor.

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- 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 IRB/IEC, in accordance with local regulations.

If an AE initially non-serious worsens and becomes an SAE, 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 events recording in Section 8.7, 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 the page to the sponsor via a secure system.

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 guidance, the assessment of the seriousness and the causality of AEs 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 AEs and the causality of (at least) the serious AEs, 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, the Sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH GCP guidelines and local regulations, to the appropriate Authorities, to all the Investigators involved and to the trial subjects involved - through the Investigators - as mentioned in Section 13.4 (Modification of the information and consent form).

The concerned Authorities will be notified as soon as possible by the Sponsor of the DSMB recommendations if any, where relevant for the safety of subjects (*i.e.* modification or termination of the study).

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8.10 Responsibilities of Data Safety Monitoring Board

Considering the limited data available on the safety of calaspargase pegol in adults older than age 30 years, the greater likelihood of asparaginase-class toxicities occurring with increasing age, and the vulnerability of the treated population, a DSMB has been set up to review patient safety data throughout the study to ensure that the patients' potential benefit is not compromised by safety concerns. In accordance with the DSMB charter and the rules for DSMB functioning, the DSMB is an independent group of experts who provide expertise and recommendations to the Sponsor. Their primary responsibility is to review safety data in the light of the benefit-risk ratio on a regular basis. After each meeting they will provide written recommendations regarding the progress and conduct of the study (continuation, modification or termination). The DSMB could also give recommendations on the possible modification of the study protocol based on the review of the safety data, and suspend or terminate the study early in case of serious concerns about patient safety. The DSMB members will ensure their availability in case of any required extraordinary meeting.

8.11 Management of Treatment Dose Adaptations due to Toxicities

Dose modification recommendations for calaspargase pegol are summarized in Table (8.11) 1.

For the NIMPs, the management of the toxicities has to be done according to the corresponding United States prescribing information (USPI).

Table (8.11) 1 - Management of Calaspargase pegol-associated Toxicities

Worst Toxicity CTCAE Grade (unless otherwise specified)	**Recommended Action**
Hypersensitivity/Infusion Reaction	
Grade 1	Reduce the infusion rate by 50%
Grade 2	Interrupt the calaspargase pegol infusion; treat the symptoms; when symptoms resolve, resume the infusion and reduce the infusion rate by 50%
Grade ≥3	Grade 3 hypersensitivity corresponding to allergic/anaphylactic reaction characterized by symptomatic bronchospasm with or without urticaria; or allergy-related edema/angioedema; or hypotension AND requiring corrective parenteral treatment with IV antihistamines, cortisone or adrenaline. Permanently stop calaspargase pegol and treat the symptoms
Liver Toxicity	
Increase in AST and/or ALT	
Grade 3 (> 5.0 – 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal)	Hold calaspargase pegol until values ≤ Grade 2
Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal)	Hold calaspargase pegol until values ≤ Grade 2. Repeat laboratory tests weekly. If AST and/or ALT do not return to ≤ Grade 2 and there is a ≥ 28-day delay in the start of the next scheduled cycle of chemotherapy, then permanently discontinue calaspargase pegol
Increase in Direct bilirubin	
Direct bilirubin ≥ 3.1 mg/dL	Hold calaspargase pegol until direct bilirubin is < 2.0 mg/dL. Repeat laboratory tests weekly. Permanently discontinue calaspargase pegol if direct bilirubin does not return to < 2 mg/dL and requires a ≥ 28-day delay in the start of the next scheduled cycle of chemotherapy.

Worst Toxicity CTCAE Grade (unless otherwise specified)	**Recommended Action**
Pancreatitis	
Increase in lipase and/or amylase > 3 x ULN without symptoms	Hold calaspargase pegol until enzymes are stabilized or decreased
Pancreatitis Grade ≥ 3	Permanently discontinue calaspargase pegol
A CT scan or other imaging test to assess the pancreas, liver, and gallbladder may be performed within 1 week of the first occurrence of any Grade ≥ 3 amylase and/or lipase increase, or as clinically indicated	
Hemorrhage	
Grade 2 with hypofibrinogenemia	Hold calaspargase pegol for Grade ≥ 2 hemorrhage with hypofibrinogenemia until toxicity is Grade ≤ 1. Do not withhold calaspargase pegol for abnormal laboratory findings without a clinical correlate. Consider cryoprecipitate to keep fibrinogen > 100 mg/dL only if patient is actively bleeding, at high risk of bleeding while on full-dose anticoagulation, or undergoing an invasive procedure. Do not otherwise replete fibrinogen as cryoprecipitate and fresh frozen plasma (FFP) are prothrombotic agents*
Grade ≥ 3	Hold calaspargase pegol until bleeding ≤ Grade 1, until acute toxicity and clinical signs resolve, and coagulant replacement therapy stable or completed
Grade 4 CNS bleeding	Permanently discontinue calaspargase pegol; treat the symptoms as clinically indicated
Thrombosis (Thromboembolic Events)	
Grade 3 Non-CNS Thrombosis	Hold calaspargase pegol until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed; do not withhold for abnormal laboratory findings without a clinical correlate Work up for additional hypercoagulable conditions should be considered; discuss additional anticoagulant therapy with study Principal Investigator
Grade 4 Non-CNS Thrombosis	Hold calaspargase pegol until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed or withdrawal at Investigator discretion
Grade 2 CNS Thrombosis	Hold calaspargase pegol if there are any clinical symptoms, treat the patient with antithrombotic therapy. Calaspargase pegol can be resumed when symptoms associated with the event are resolved and after imaging demonstrates clot stabilization or improvement.
Grade ≥ 3 CNS Thrombosis, or Pulmonary Embolism or Intracardiac Thrombus	Permanently discontinue calaspargase pegol
Hypertriglyceridemia	
Serum triglyceride ≤ 1000 mg/dL	Continue calaspargase pegol but monitor closely for pancreatitis and consider adding omega 3 fatty acids, fenofibrate and/or a statin.
Serum triglyceride > 1000 mg/dL	In case of severe asymptomatic hypertriglyceridemia (*i.e.*, triglyceride levels of > 1000 mg/dL and no association with acute pancreatitis), as first line therapy, dietary intervention followed by fibrates or other treatment of Investigator's choice, including plasmapheresis, may be considered. Administration of calaspargase pegol will be left to the discretion of the Investigator

Worst Toxicity CTCAE Grade (unless otherwise specified)	**Recommended Action**
Hyperglycemia	
Grade ≥ 3	Hold glucocorticoids until blood glucose is regulated with insulin
Ketoacidosis	Follow institutional guidelines; Consider: - Holding calaspargase pegol and dexamethasone until blood glucose can be regulated with insulin. Therapy may then be resumed at the previous dose. - Not modifying calaspargase pegol or dexamethasone dose for uncomplicated hyperglycemia. Treat with insulin to maintain normal blood glucose levels.

**Consult study Principal Investigator as necessary.*
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; CT = computerized tomography; IV = intravenous; ULN = upper limit of normal

8.12 Additional Precautions for Calaspargase Pegol Use

8.12.1 Hepatic Veno-occlusive Disease (VOD)

Hepatic VOD is a rare, life-threatening, disease that can cause hepatic damage and is a complication of certain chemotherapy regimens, pre-transplant. Cases of hepatic VOD have been observed with calaspargase pegol in the post-marketing setting in combination with standard chemotherapy. Signs and symptoms of hepatic VOD include rapid weight gain, fluid retention with ascites, hepatomegaly, and rapid increase of bilirubin. **Patients with a history of VOD are excluded from Part 2 of the study**.

9 OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY AND SAFETY

9.1 Assessments Related to Selection/Inclusion Criteria

9.1.1 Screening Assessments

The assessments to be performed at screening, including those to determine that subjects meet the inclusion criteria relating to their disease status, are listed in Section 8.2.1.

9.1.2 Sample Collection

The blood sample is to be collected within 7 days of inclusion.

9.2 Plasma Asparaginase Activity/Pharmacokinetics/Pharmacodynamics and Therapeutic Drug Monitoring

9.2.1 Plasma Asparaginase Activity/Pharmacokinetics/Pharmacodynamics

The assessment of calaspargase pegol is characterized by measurement of PAA, *i.e.* the activity of the medicinal product, and not the actual molecular amount of medicinal product.

9.2.1.1 Sample Collection Time Points

Blood samples for the evaluation of PAA/PK/PD are to be collected at the time points listed in Table (9.2.2.1) 1. The accurate sampling dates and times must be recorded in the eCRF.

Table (9.2.1.1) 1 - Sample Collection Time Points for Plasma Asparaginase Activity

Study Phase	Study Phase Day[1]	Timing of Sample[1]	Window
Remission Induction	4	before calaspargase pegol infusion start	within 4 hours before infusion start
	5	24 hours after the end of infusion	± 4 hours
	6	48 hours after the end of infusion	± 4 hours
Remission Consolidation	15	before calaspargase pegol infusion start	within 4 hours before infusion start
	16	24 hours after the end of infusion	± 4 hours
	43	before calaspargase pegol infusion start	within 4 hours before infusion start
	44	24 hours after the end of infusion	± 4 hours
Interim Maintenance	22	before calaspargase pegol infusion start	within 4 hours before infusion start
	23	24 hours after the end of infusion	± 4 hours
Delayed Intensification	4	before calaspargase pegol infusion start	within 4 hours before infusion start
	5	24 hours after the end of infusion	± 4 hours
	43	before calaspargase pegol infusion start	within 4 hours before infusion start
	44	24 hours after the end of infusion	± 4 hours

1: Timing of samples are related to the calaspargase pegol infusion and must be adapted in case of change in the day of administration

9.2.1.2 Sample Collection

In all participants, 2.5 mL of blood will be taken at each time point for PAA/PK/PD assessment, leading to a total volume of 32.5 mL (13 time points overall). PAA will be determined in sodium heparinized plasma, using a coupled enzymatic activity assay, validated according to current regulatory guidelines.

9.2.2 Therapeutic Drug Monitoring

TDM will be based on the measurement of PAA after each calaspargase pegol administration and will be performed at a centralized laboratory (BioAgilytix).

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9.2.2.1 Sample Collection Time points

TDM will be done 7-, 14-, and 21-days post dose in each phase to monitor for adequate asparagine depletion demonstrated by PAA ≥ 0.1 U/mL. Blood samples for TDM are to be collected at the time points shown in Table (9.2.2.1) 1. The accurate sampling dates and times must be recorded in the eCRF.

Table (9.2.2.1) 1 - Sample Collection Time Points for Therapeutic Drug Monitoring

Study Phase	Study Phase Day[1]	Days Post-calaspargase pegol Infusion[1]
Remission Induction	11	7
	18	14
	25	21
Remission Consolidation	22	7
	29	14
	36	21
	50	7
	57	14
	64	21
Interim Maintenance	29	7
	36	14
	43	21
Delayed Intensification	11	7
	18	14
	25	21
	50	7
	57	14
	64	21

1) Timing of samples are related to the calaspargase pegol infusion and must be adapted in case of change in the day of administration

9.2.2.2 Sample Collection

In all participants, 2.5 mL of blood will be taken at each time point for TDM assessment, leading to a total volume of 45 mL (18 time points overall). PAA for TDM will be determined using a coupled enzymatic activity assay, validated according to current regulatory guidelines.

9.3 Immunogenicity

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

This evaluation will be based on qualitative enzyme-linked immunosorbent assays (ELISA) using calaspargase pegol as coating antigen. The assays followed a multi-tiered approach consisting of a screening assay, a confirmatory assay, a titer assay and a specificity assay. All positive samples will be further confirmed by competitive ELISA for the presence of binding antibodies against calaspargase pegol. Samples, confirmed positive, will then be assayed for antibodies against PEG. For all these assays, antibody status (negative or positive) 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 ADA titer.

Due to the format of the PK assay which directly measures the asparaginase activity, the neutralizing potential of anti-drug antibodies in positive samples will be evaluated based on the concomitant results of the asparaginase activity assay.

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9.3.1 Sample Collection Time Points

Blood samples for evaluation of ADA are to be collected at the time points shown in Table (9.3.1) 1.

Table (9.3.1) 1 - Sample Collection Time Points for Immunogenicity

Study Phase	Study Phase Day[1]	Timing of Sample[1]	Window
Remission Induction	4	Before calaspargase pegol infusion start	Within 4 hours before infusion start
	18	14 days post-calaspargase pegol infusion	Within the planned day
	29	at end of induction	Within the planned day
Remission Consolidation	15	Before calaspargase pegol infusion start	Within 4 hours before infusion start
	43	Before calaspargase pegol infusion start	Within 4 hours before infusion start
Interim Maintenance	22	Before calaspargase pegol infusion start	Within 4 hours before infusion start
Delayed Intensification	4	Before calaspargase pegol infusion start	Within 4 hours before infusion start
	43	Before calaspargase pegol infusion start	Within 4 hours before infusion start
End of study or Early Discontinuation		End-of-Treatment	365 days post the initial dose ±7 days, within the planned day
		Early Discontinuation	30 days after the last calaspargase dose

1) Timing of samples is related to the calaspargase pegol infusion and must be adapted in case of change in the day of administration

9.3.2 Sample Collection

In all participants, 2.5 mL of blood will be taken at each time point for ADA assessment leading to a total volume of 22.5 mL (9 time points overall). ADA assessment will be carried out in sodium heparinized plasma using an ELISA-based assay, validated according to current guidelines, with respect to cut-point, precision, linearity, short-term stability, freeze-thaw stability and drug interference.

9.4 Assessment of Biomarkers

BMA/exploratory (central testing) samples will be collected at Screening and at EOT (per investigator's discretion) or relapse (per investigator's discretion). Biomarkers will be analyzed include, but are not limited to, the analysis of common genomic abnormalities in ALL disease.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sampling collection or not perform or discontinue an analysis due to practical, scientific, or strategic reasons (*e.g.*, inadequate sample number, issues related to the quality of the sample, issues related to the assay that preclude analysis, or impossibility to perform correlative analyses). Therefore, depending on the results obtained during the study, sample collection may be omitted at the discretion of the Sponsor.

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9.5 Future research

9.5.1 Mandatory Retention (Part 2 Only)

Samples collected for measuring antidrug antibodies will be stored, for a maximum of 5 years after the end of the study. This allows the sponsor to perform additional analyses related to immunogenicity in case of Regulatory Authorities' request.

9.5.2 Optional Future Research

With patient consent, the remaining BMA and blood samples will be transferred to a central biorepository to be stored for a maximum of 15 years after the end of the study. The samples could be further analyzed to address scientific questions related to the product or disease, including research related to improvements or enhancements in the development of bioanalytical methods restricted to the study of the pathology and response to treatment. Patient consent can be withdrawn at any time without compromising participation in the overall clinical study investigations. In case of consent withdrawal from optional sample storage, related samples will be destroyed before further optional assessments are completed.

10 STATISTICS

The statistical analysis methods for safety, efficacy, PK/PD and immunogenicity 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 Statistical Analysis

10.1.1 Analysis Data Sets

10.1.1.1 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.

10.1.1.2 Primary Nadir Plasma Asparaginase Activity Analysis Set

The primary nadir plasma asparaginase activity (PNPAA) endpoint refers to the PAA 21 days after the consolidation Day 43 dose. The PNPAA analysis set (PAS) will include all evaluable patients in Part 1 and Part 2 in the combined patient groups (aged 22 to 39 years and BMI $\leq$ 35 kg/m² + aged 40 to 54 years and BMI $\leq$ 35 kg/m²) who are treated at the recommended dose levels.

Subjects will not be evaluable for the PNPAA analysis if:
- They received at least 1 dose different from the corresponding recommended Part 2 dose before and including the consolidation Day 43 dose.
- They 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 ADA before the consolidation Day 43 dose; or
- Had any other factors that may impact the interpretability of the PNPAA analysis.

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10.1.1.3 Per-protocol Analysis Set

The per-protocol analysis set (PPAS) will include all subjects in the FAS population who did not have any major protocol violations. All decisions to exclude subjects from the PPAS will be made prior to the database lock for the final analysis and the rules will be included in a separate document.

10.1.1.4 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/PD analysis. The PK/PD dataset will include only the subjects who had sufficient samples collected to provide interpretable PK/PD results with no deviations that might have affected the PK/PD interpretation.

10.1.1.5 Immunogenicity Analysis Set

The immunogenicity analysis set 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.

10.1.2 Analysis Methods

Unless otherwise specified, all analyses will be conducted by patient group and dose if estimable. Dose level designation for each patient is determined based on the first dose that patient received.

10.1.2.1 Safety Analysis

Safety for patients treated at recommended doses will also be summarized by higher dose groups, lower dose groups and overall in the FAS.

10.1.2.1.1 Adverse Events

Treatment emergent AEs will be assessed according to the NCI CTCAE v5.0. Laboratory abnormalities will be classified into Common Terminology Criteria (CTC) grade according to CTCAE v5.0 and will be reported as AEs.

Adverse events will be summarized for the FAS in hierarchical tables, presenting the number and percentage of patients having at least 1 AE, and having at least 1 AE in each primary system organ class and for each preferred term using Medical Dictionary for Regulatory Activities (MedDRA) coding. AEs will be sorted by descending frequency, and alphabetically where frequency is tied. Such summaries will be produced for all AEs, 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 summaries will be by system organ class, preferred term, treatment phase 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 AEs will be listed, and any other information collected (*e.g.*, start/end dates and duration of AE, severity or relatedness to study medication) will be listed as appropriate.

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AEs of special interest will be analyzed 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. 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.

10.1.2.1.2 Other Safety Evaluations

Descriptive statistics of laboratory parameters and continuous variables of vital signs will be calculated for each time point. 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 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 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.

10.1.2.1.3 Treatment Exposure

Duration of exposure, cumulative dose, total number of doses administered, relative dose intensity (RDI), actual dose intensity (DI) and planned dose intensity (PDI) will be summarized. Frequency counts and percentages of subjects who have dose reductions or interruption, and the corresponding reasons, will be provided. The number of dose delays per subject, and the duration of dose delays will be summarized. Duration of follow-up will also be summarized.

Listings of all doses of the study drug along with dose change/interruption reasons will be provided.

10.1.2.2 Plasma Asparaginase Activity Analyses

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.

Other PAA endpoints for patients treated at recommended doses will also be summarized by 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 levels and overall, in the FAS. 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.

10.1.2.3 Other Efficacy Analyses

Other efficacy endpoints for patients treated at recommended doses will also be summarized by 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 levels and overall, in the FAS.

The number and proportion of subjects achieving CR will be summarized.

The frequency and proportion with a 2-sided 95% Clopper-Pearson CI of end-induction and end-consolidation MRD status will be summarized.

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10.1.2.3.1 Event-free Survival

Event-free survival is defined as time from the first dose of calaspargase pegol to the date of induction failure, 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. Additional censoring rules and sensitivity analysis for EFS may be specified in the Statistical Analysis Plan (SAP).

10.1.2.3.2 Disease-free Survival

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. Details including censoring rules will be provided in the SAP.

10.1.2.3.3 Overall Survival

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.

The OS rate, EFS rate and DFS rate at 1 year, 2 years and 3 years will be calculated along with the 95% CIs estimated using the Kaplan-Meier method, respectively.

10.1.2.4 Population Analysis

10.1.2.4.1 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 treatment and by the primary reason for discontinuation by treatment phase, completed protocol therapy, discontinued protocol therapy and by the primary reason for discontinuation by treatment phase, completed post-treatment follow-up, discontinued post-treatment follow-up and reason for discontinuation.

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

10.1.2.4.2 Demographics

Descriptive statistics will be summarized for demographics, including age, age groups (22-39, 40-< 55, ≥ 55 years), sex, ethnicity, race, weight, height, BMI, and BSA.

10.1.2.4.3 Baseline Characteristics

Descriptive statistics will be summarized for baseline characteristics.

10.1.2.5 Exploratory Analysis

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

The primary and secondary analyses may be conducted for each age or dose group if estimable.

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10.1.2.6 Handling of Missing, Unused, and Spurious Data

Adverse Events
Handling of unknown causality assessment: If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related".

Handling of unknown severity grades: The unknown 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".

Immunogenicity
Missing baseline ADA results will be imputed as negative. If all ADA results before consolidation Day 43 dose were missing for a patient, that patient will not be considered evaluable for PNPAA analysis.

10.1.3 Specified Analyses for Independent Data Safety Monitoring Board Review

In completed Part 1 of the study, the DSMB evaluated the safety and available PAA data for each of the study run-in cohorts and provided recommendations whether to confirm or adjust the proposed calaspargase doses.

In Part 2 of the study the DSMB will meet periodically, consistent with the DSMB Charter, or more frequently if required to review toxicity and enrollment data. Information provided to the committee may include: up-to-date subject enrollment; toxicity information; all Grade 3 or higher unexpected AEs that have been reported; summary of all deaths on study; and a summary provided by the study team. Other information (*e.g.*, scans, laboratory values) may be provided upon request.

10.1.4 Procedures for Reporting Changes to the Planned Analysis

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

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10.2 Determination of Sample Size

The study consists of 2 parts for each of the 4 patient groups. For each patient group, Part 1 was a dose-confirmation run-in period with approximately 4-8 patients, and patients in Part 2 will be treated at the corresponding recommended dose.

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 assumption for 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 higher dose patients treated at the recommended doses are required to provide at least 90% power.

At the end of the Part 1, two subjects were evaluable for NPAA to be included in the Primary Nadir Plasma Asparaginase Activity Analysis Set (described in Section 10.1.1.2).

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 (10.2) 1. 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 (10.2) 1 - Sample Size Justification for Safety Analysis

Adverse Event of Special Interest	Incidence Rate: Historical Estimate	Observed Incidence Rate Assuming 10% Increase	80% Clopper-Pearson Confidene 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.

10.3 Pharmacokinetic and Pharmacodynamic Analyses

10.3.1 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 TDM will be pooled for the PK/PD analysis as they both provide information on PAA measurements that support the analysis.

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A population modeling approach will be used to describe the PK/PD/PAA in patients from the present study.

Individual PK parameters such as area under the plasma asparaginase activity-time curve (AUC) or maximum observed plasma asparaginase activity (C_{max}) will be derived using the population PK model.

The population modeling analysis will be described in a separate data analysis plan (DAP).

10.3.2 Pharmacokinetic/Pharmacodynamic Interpretation for Efficacy and Safety

Exploratory assessment of the relationship between individual PK parameters and PD endpoints for efficacy (such as MRD status) or safety (such as occurrence of AEs) might be performed. If applicable, a separate DAP will be written.

10.3.3 Immunogenicity Analysis

The assessment of anti-drug antibodies includes binding antibodies to calaspargase pegol and binding anti-PEG antibodies.

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 predose 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 as follows:
- Parmacokinetics: through the temporal association of antibodies with the loss of asparaginase activity.
- Safety: through the potential relationships with treatment–emergent hypersensitivity and anaphylactic reactions.

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11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/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 is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP 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.

Temporary modifications and recommendations of the sponsor in the context of the Covid-19 pandemic are described in Appendix 7.

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 organized 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 e-CRFs (i.e., access to an analogic phone line or his/her computer).
- Check that the e-CRFs, have been filled out correctly.
- Directly access source documents for comparison of data therein with the data in the e-CRFs.
- 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.

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12.2 Computerized Medical Files

If computerized 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 unauthorized access to the data and to the computer system.

If the computerized 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 computerized medical files are considered as validated by the Sponsor, the Investigator undertakes to give access to the monitor to the computerized 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, ICFs, RTSM report or equivalent document).

12.3 Audit - Inspection

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

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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 center(s). The Sponsor will inform the Investigators concerned immediately upon notification of a pending study centers 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 of the documents relevant to the study.

If the computerized 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 computerized 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 computerized 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.

12.4 Supervisory Committees

DSMB recommendations will be forwarded to the IRB/IEC/Competent Authorities only if relevant for the safety of participants.

13 ETHICS

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

The study protocol, the "Participant information and consent form" document, the "Legal representative information and consent form" document, the list of Investigators document, the insurance documents, the prescribing information USPI or Investigator's Brochure of administered IMPs and NIMPs will be submitted to (an) IRB(s)/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 center before written approval by corresponding IRB/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 1), 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.

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The Investigator or a person designated by him/her is to collect written consent from each participant before his/her participation in the study. Prior to this, the Investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs. 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 consent at any time.

The participant will be provided with an information and consent form (ICF) in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One or two original (depending on local regulations) copies of the ICF must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant 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 will be given 1 signed original (or copy) of the ICF, the (second) original will be kept by the Investigator.

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

Informed Consent for Tissue Biobanking
A separate consent may be required for participating in the optional long-term storage and optional analysis of blood, BMA samples (biorepository). This consent may be withdrawn at any time without compromising the patient's participation in the overall clinical study.

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 IRB/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 IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment and/or his/her legally acceptable representative or an independent witness must complete, date and sign 1 or 2 originals (depending on local regulations) of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive 1 signed original (or copy, where applicable) of the amendment to the information and consent form.

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14 DATA HANDLING AND RECORD KEEPING

14.1 Study Data

A 21 CFR Part 11-compliant electronic data capture system is used for this study. An 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. or the contract research organization (CRO), other structure 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 or the CRO, other structure.

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 center to the study database.

The Investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, in a timely manner, 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 4.5) 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 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 authorized 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 data if deemed via a request to the Sponsor.

The investigator or authorized member for sign-off must confirm the authenticity of the data recorded in the e-CRF by signing the e-CRF in a timely manner as defined in the e-CRF completion guide.

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 from his/her center for archiving it in the study file (see Section 14.3).

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14.2 Data Management

Data are collected via an e-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 the central laboratory, the Clinical Data Management of I.R.I.S. is responsible for data transfer: centralized laboratory provides electronic transfer of computerized 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.

The Medical Review Department of I.R.I.S. or a contract research organization (CRO), if subcontracted, other structure is responsible for data coding including:

- Medical /surgical history, AEs and procedures using MedDRA.
- Medications using the WHO 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 IRB/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.

All data for participants recruited for the trial will be entered onto the e-CRFs via an electronic data capture (EDC) system provided by the sponsor or designee. Only authorised staff may enter data onto the e-CRFs. If an entry error is made, the corrections to the e-CRFs will be made according to e-CRF guidelines by an authorised member of the site staff. Any discrepancies will be noted in the e-CRF system by means of electronic data queries. Authorised site staff will be asked to respond to all electronic queries according to the e-CRF guidelines. Access to the EDC system will be controlled, and a complete audit trail of all data changes will be maintained.

In case of data generated by centralised laboratory, central reading centre, e-PRO/e-COA or service provider, the service provider(s) provide(s) electronic transfer of data to sponsor or designeeaccording to transfer specifications.

All data collected are stored in a secured database. This database is locked, unblinded if applicable and made available for statistical analysis at the end of the study or in case of interim analysis

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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.

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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 multicenter one, the first publication must be performed only with data collected from several centers and analyzed under the responsibility of I.R.I.S. The Investigator commits himself not to publishing or communicating data collected in only 1 center or part of the centers 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.
- 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 1 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.

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

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study. The results will be submitted for publication in scientific literature within 18 months after the end of the study.

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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.

With the agreement of the participant, the Investigator will inform the participant's general practitioner about his/her patient's participation in a clinical study.

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 IRB/IEC that examined the initial protocol. They can only be implemented after a favorable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of 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 IRB/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 authored in compliance with I.R.I.S. standard operating procedures.

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 1 year after the end of the study.

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17.2 Concerning the Sponsor

The Sponsor undertakes to:
- Supply the Investigator with adequate and sufficient information concerning the IMP(s) and the NIMP(s) administered during the study to enable him/her to carry out the study.
- Supply the Investigator with Investigator's brochure if the test drug is not marketed.
- Supply the Investigator with USPI, the one best suited to ensure participant safety, and any potential updated version during the study:
  - For the test drug, appended to Investigator's brochure (Section 4. Guidance for the Investigator.
  - For all NIMPs available on the market.

Obtain any authorization to perform the study and/or import license for the IMP(s) administered that may be required by the local authorities before the beginning of the study.

Provide the Investigator or Coordinator(s) annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/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 authorization 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 Chief Information Security Officer, Data Protection Officer, 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 calaspargase pegol and study CL2-95015-001 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 a 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 8).

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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 authorization 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 Organization of the Center

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 center (cardiologist, pharmacist) must figure in the "Site Signature and Delegation of Responsibilities Log".

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 center.

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 IRB/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).

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19 APPENDICES

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Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

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9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

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Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

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Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

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31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

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Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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Appendix 2: Patient Performance Status

Status Karnofsky	**Grade**	**Status ECOG* - ZUBROD / WHO**
Normal, no complaints; no evidence of disease.	100 0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90	
Normal activity with efforts; some signs or symptoms of disease.	80 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work.
Cares for self; unable to carry on normal activity or to do active work.	70	
Requires occasional assistance, but is able to care for most of his personal needs.	60 2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	
Disabled; requires special care and assistance.	40 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospital admission is indicated although death not imminent.	30	
Very sick; hospital admission necessary; Active supportive treatment necessary.	20 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Moribund; fatal processes progressing rapidly.	10	
Dead	0 5	Dead

** As published in Oken M.M., Creech R.H., Tormey D.C., Horton J., Davis T.E., McFadden E.T., Carbone P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.*

Appendix 3: MDRD Formula

MDRD formula (Levey *et al*, 2006)
The re-expressed 4-variable MDRD study equation for GFR, expressed in L/min/1.73m^2, with serum creatinine (Scr) expressed in mg/dL, is as follows:

GFR (mL/min/1.73 m^2) = 175 x (Scr)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if black)

The re-expressed 6-variable MDRD Study equation for GFR, expressed in mL/min/1.73m^2, is as follows with serum creatinine (Scr) expressed in mg/dL and urea nitrogen (SUN) expressed as mg/dL, is as follows:

GFR (mL/min/1.73 m^2) = 161.5 x (Scr)$^{-0.999}$ x (age)$^{-0.176}$ x (SUN)$^{-0.17}$ x (albumin)$^{-0.318}$ x (0.762 if female) x (1.18 if black)

Cockcroft formula (Cockcroft *et al*, 1976)

CreatClear [mL/min] = ((140 – Age [years]) / SerumCreat [µmol/L]) * Weight [kg]* Sex

Male = 1.23
Female = 1.04

Appendix 4: Backbone Chemotherapy Drug Information (Non-Investigational Medicinal Products)

The backbone regimen drugs will be administered according to the schedule based on that used in the CALGB 10403 protocol (See Figure (4.1.1) 1). They will be considered non-investigational medicinal products (NIMPs) and will not be provided by the Sponsor.

NOTE: For complete product information on each of the backbone chemotherapy agents used, please consult the medical reference texts such as the Physicians' Desk Reference, the FDA website or your local institution's pharmacist.

It is acceptable for individual chemotherapy doses to be delivered within a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new course/cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (*e.g.*, serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

General Considerations

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses of chemotherapy due to changes in weight unless the calculated dose changes by ≥ 10% on day 1 of each course or cycle.

A list of the adverse events and potential risks associated with the commercial agents is provided for each product below. For complete adverse event information please refer to the individual agent's product information (reference provided for each backbone agent).

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CYTARABINE INTRATHECAL (CYTOSAR®, ARA-C) (NSC #63878)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection, solution [preservative free]: 20 mg/mL (5 mL, 50 mL); 100 mg/mL (20 mL).

Preparation, Storage and Stability

Store intact vials of solution at room temperature 15ºC to 30ºC (59ºF to 86ºF). Intrathecal dilutions are preservative-free and should be used as soon as possible after preparation (reconstitute with preservative-free normal saline [NS] to preferred final volume if necessary). Each clinic/institution shall establish procedures to prevent errors with intrathecal administration. Intrathecal medications should NOT be prepared during the preparation of any other agents. After preparation, store intrathecal medications (until use) in an isolated location or container clearly marked with a label identifying as "intrathecal" use only. Intrathecal preparations should be administered as soon as possible after preparation and no later than 24 hours after preparation (or sooner, as per institutional guidelines).

Administration

- Refer to the treatment section for specific dosing and administration instructions. Cytarabine intrathecal administration requires medication safety procedures:
- Intrathecal medication should not be prepared during the preparation of any other agents.
- After preparation, store in an isolated location or container clearly marked with a label identifying as "intrathecal" use only.
- Delivery to the patient should only be with other medications intended for administration into the central nervous system.

Note: Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area. CSF volume correlates with age and not to BSA.

Adverse Events

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Known potential adverse events associated with intrathecal cytarabine administration include:

- Central nervous system: fever, necrotizing leukoencephalopathy (with concurrent cranial irradiation, intrathecal methotrexate, and intrathecal hydrocortisone), neurotoxicity, paraplegia.
- Gastrointestinal: nausea, vomiting.
- Ocular: Blindness (with concurrent systemic chemotherapy and cranial irradiation).

Drug Interactions

Intrathecal dosing, drug interactions are not anticipated.

Pharmacokinetics

Intrathecal dosing, no information available.

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Nursing Guidelines

- Can be a potent myelosuppressive agent. Monitor CBC closely. Anemia, leukopenia, and thrombocytopenia are expected. Nadir within 5-7 days with recovery expected in 2-3 weeks.
- Nausea and vomiting are dose-related, common, and often preventable with antiemetic drugs. Administer as ordered and assess for their effectiveness.
- Stomatitis is possible.
- Monitor LFTs-elevations of LFT's may occur.
- Cerebellar toxicity can occur in 16-40% of patients with more severe symptoms at higher doses. Monitor for these toxicities with each dose of ARA-C. Signs and symptoms of cerebellar toxicity can include: lethargy with progressive confusion, ataxia, nystagmus, slurred speech. Report any of these or other neurological changes to the MD immediately.
- Instruct patient to report any shortness of breath or difficulty breathing as this may be a sign of a rare but life-threatening pulmonary complication.
- Monitor for signs of conjunctivitis and/or keratitis. This is usually prevented with prophylactic glucocorticoid eye drops.
- Assess for skin rash. This may present itself as an erythema without exfoliation, or a generalized rash. Report to MD.
- Monitor for "ARA-C" syndrome. This is characterized by bone and muscle pain, chest pain, fever, general weakness, reddened eyes, and skin rash. Report these to the MD, as patient may need to be treated with corticosteroids.

CYTARABINE INTRAVENOUS/SUBCUTANEOUS (CYTOSAR®, ARA-C) (NSC #63878)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection, powder for reconstitution: 100 mg, 500 mg, 1 gram, 2 gram. Commercially available solution for injection in concentrations of 20 mg/mL and 100 mg/mL. Commercially available preparations may be preservative-free or preservative-containing.

Preparation, Storage and Stability

Store intact vials of powder at room temperature 15ºC to 30ºC (59ºF to 86ºF). Reconstitute with bacteriostatic water for injection. Reconstituted solutions are stable for up to 8 days at room temperature, although the manufacturer recommends use within 48 hours. Further dilution in 250-1000 mL of D5W or 0.9% sodium chloride (NaCl) is stable for 8 days at room temperature (25°C). Note: Solutions containing bacteriostatic agents should not be used for the preparation of either high doses or intrathecal doses of cytarabine.

Administration

Refer to the drug treatment section 6.4 of the protocol for specific administration directions. May be given IV or subcutaneously.

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Adverse Events

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Cytarabine is a potent Myelosuppressive agent. Myelosuppression is dose and schedule dependent with nadir in 5–7 days and recovery in 2–3 weeks (6 weeks for high dose). Infectious complications following injection (Viral, bacterial, fungal, parasitic, or saprophytic infections) can be occurred.

Most frequent potential toxicities include:
- Central nervous system: Fever.
- Dermatologic: Rash.
- Gastrointestinal: Anal ulceration and inflammation, anorexia, diarrhea, nausea, vomiting.
- Hematologic: Myelosuppression (including neutropenia, anemia, thrombocytopenia, leukopenia), bleeding, megaloblastosis, reticulocytes decreased.
- Hepatic: Hepatic dysfunction.
- Local: Thrombophlebitis.

Less frequent known potential toxicities include:
- Cardiovascular: Chest pain, pericarditis, sinus bradycardia.
- Central nervous system: Dizziness, headache, neural toxicity, neuritis.
- Dermatologic: Alopecia, pruritus, skin freckling, skin ulceration, urticaria.
- Gastrointestinal: Abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat.
- Genitourinary: Urinary retention.
- Hepatic: Jaundice.
- Local: Injection site cellulitis.
- Ocular: Conjunctivitis.
- Renal: Renal dysfunction.
- Respiratory: Shortness of breath, pneumonia.
- Miscellaneous: Allergic edema, anaphylaxis, sepsis.

Drug Interactions
- Cytochrome P450 Effect: None known.
- Increased Effect/Toxicity: Cytarabine may increase the levels/effects of: Clozapine, Leflunomide, Natalizumab, Vaccines (Live). The levels of Cytarabine may be increased by: Denosumab, Pimecrolimus, Roflumilast, Tacrolimus (Topical); Trastuzumab.
- Decreased Effect: Cytarabine may decrease the levels/effects of: BCG, Cardiac Glycosides, Coccidioidin Skin Test, Flucytosine, Sipuleucel-T, Vaccines (inactivated); Vaccines (live).
- Herb/Nutraceutical Interactions: Avoid Echinacea.
- Pharmacokinetics.
- Distribution: volume of distribution (Vd): Total body water; widely and rapidly since it enters the cells readily; high-dose cytarabine crosses the blood-brain barrier with CSF levels of 40% to 50% of plasma level.
- Metabolism: Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to ara-cytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside.
- Half-life elimination: IV: Initial: 7-20 minutes; Terminal: 1-3 hours.
- Excretion: Urine (~80%) within 24 hours.

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Nursing Guidelines

- Can be a potent myelosuppressive agent. Monitor CBC closely. Anemia, leukopenia, and thrombocytopenia are expected. Nadir within 5-7 days with recovery expected in 2-3 weeks. Hematological toxicity is more intense if ARA-C is given as a continuous IV infusion versus an IV bolus.
- Nausea and vomiting are dose-related, common, and often preventable with antiemetic drugs. Administer as ordered and assess for their effectiveness.
- Instruct patient of possibility of metallic taste. The use of sugarless hard candies may lessen this effect.
- Stomatitis is possible.
- May cause pancreatitis or peritonitis. Instruct patient to report any severe or worsening abdominal pain immediately.
- Monitor LFTs-elevations of LFT's may occur.
- Cerebellar toxicity can occur in 16-40% of patients with more severe symptoms at higher doses. Monitor for these toxicities with each dose of ARA-C. Signs and symptoms of cerebellar toxicity can include: lethargy with progressive confusion, ataxia, nystagmus, slurred speech. Report any of these or other neurological changes to the MD immediately.
- Instruct patient to report any shortness of breath or difficulty breathing as this may be a sign of a rare but life-threatening pulmonary complication.
- Monitor for signs of conjunctivitis and/or keratitis. This is usually prevented with prophylactic glucocorticoid eye drops.
- Assess for skin rash. This may present itself as an erythema without exfoliation, or a generalized rash. Report to MD.
- Monitor for "ARA-C" syndrome. This is characterized by bone and muscle pain, chest pain, fever, general weakness, reddened eyes, and skin rash. Report these to the study physician, as patient may need to be treated with corticosteroids.

CYCLOPHOSPHAMIDE (CYTOXAN®, NEOSAR®, CTX) (NSC #26271)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as: Injection, powder for reconstitution: 500 mg, 1 gram, 2 gram

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature. Reconstitute vials with sterile water, normal saline, or D5W to a concentration of 20 mg/mL. Reconstituted solutions are stable for 24 hours at room temperature and 6 days under refrigeration. Further dilutions in D5W or 0.9% NaCl are stable for 24 hours at room temperature and 6 days at refrigeration.

Administration

Refer to the treatment section for specific administration instructions. Cyclophosphamide is usually administered IV Piggy Back or continuous I.V. infusion; may also be administered slow IV Push in doses ≤ 1 gram.

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Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:
- Dermatologic: Alopecia.
- Gastrointestinal: Nausea and vomiting, anorexia, diarrhea, abdominal discomfort or pain, hemorrhagic colitis, oral mucosal ulceration and jaundice.
- Hematologic: Neutropenia with or without fever.

The following include adverse reactions have been identified from clinical trials or post-marketing surveillance:
- Hypersensitivity.
- Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections.
- Urinary Tract and Renal Toxicity.
- Cardiotoxicity.
- Pulmonary Toxicity.
- Secondary Malignancies.
- Veno-occlusive Liver Disease.
- Embryo-Fetal Toxicity.

Drug Interactions
- Cytochrome (CYP) P450 Effect: Substrate of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); Inhibits CYP3A4 (weak); Induces CYP2B6 (weak), 2C8 (weak), 2C9 (weak).
- Increased Effect/Toxicity: Allopurinol may cause an increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites. CYP2B6 and CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inducers. Etanercept may enhance the adverse effects of cyclophosphamide. Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine and mivacurium.
- Decreased Effect: Cyclophosphamide may decrease the absorption of digoxin tablets. CYP2B6 and CYP3A4 inhibitors may decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inhibitors.
- Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Pharmacokinetics
- Distribution: Vd: 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia).
- Protein binding: 10% to 60%.
- Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard.
- Half-life elimination: 3-12 hours.
- Excretion: Urine (< 30% as unchanged drug, 85% to 90% as metabolites).

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Nursing Guidelines
- Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.
- Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.
- Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria. It may be necessary to catheterize and provide constant bladder irrigation.
- Advise patient in possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.
- Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.
- Report and record any complaint of lightheadedness, facial "heat sensation," diaphoresis during administration.
- Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit Cytoxan metabolism and modify its' effect. They may also increase bone marrow suppression.
- Advise female patients of possible menstrual changes or amenorrhea.
- Patients on anticoagulant therapy should have INR levels carefully monitored as cyclophosphamide increases their effect.
- Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.
- Monitor digoxin levels closely as cyclophosphamide may decrease these levels.
- Cytoxan may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

DAUNORUBICIN (CERUBIDINE®, DAUNOMYCIN, DNM) (NSC #82151)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as:
- Injection, powder for reconstitution: 20 mg.
- Injection, solution: 5 mg/mL (4 mL, 10 mL).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials of powder for injection at room temperature of 15°C to 30°C (59°F to 86°F); intact vials of solution for injection should be refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Dilute vials of powder for injection with 4 mL SWFI for a final concentration of 5 mg/mL. May further dilute in 100 mL D5W or NS. Reconstituted solution is stable for 4 days at 15°C to 25°C. Further dilution in D5W, LR, or NS is stable at room temperature (25°C) for up to 4 weeks protected from light.

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Administration
Refer to the treatment section for specific administration instructions. Daunorubicin is not for IM or SC administration. Administer as a slow IV push over 1-5 minutes into the tubing of a rapidly infusion I.V. solution of D5W or NS or dilute in 100 mL of D5W or NS and infuse over 15-30 minutes. Daunorubicin is a potent vesicant; it is best to administer IV infusion doses through a central venous access device.

Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:
Cardiotoxicity: Transient ECG abnormalities, congestive heart failure:
- Dermatologic: Alopecia (reversible).
- Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting, mucositis.
- Hematologic: Leukopenia, thrombocytopenia, anemia.
- Endocrine & metabolic: Hyperuricemia.
- Miscellaneous: Anaphylactoid reaction (rare).
- Secondary malignancies: Secondary leukemia.
- Skin: rash, urticaria, contact dermatitis, extravasation (local tissue necrosis, severe cellulitis, thrombophlebitis, or painful induration).

Drug Interactions
- Avoid Concomitant Use of Daunorubicin with any of the following: BCG; Natalizumab; Pimecrolimus; Tacrolimus (Topical); Vaccines (Live).
- Increased Effect: Daunorubicin may increase the levels/effects of: Leflunomide; Natalizumab; Vaccines (Live).
- The levels/effects of Daunorubicin may be increased by: Bevacizumab; Denosumab; PGlycoprotein inhibitors; Pimecrolimus; Tacrolimus (Topical); Taxane Derivatives; Trastuzumab.
- Decreased Effect: Daunorubicin may decrease the levels/effects of: BCG; Cardiac Glycosides; Sipuleucel-T; Vaccines (Inactivated); Vaccines (Live).
- The levels/effects of Daunorubicin may be decreased by: Cardiac Glycosides; Echinacea; PGlycoprotein Inducers.
- Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (Due to gastrointestinal [GI]).

Pharmacokinetics
- Distribution: Vd: 40 L/kg; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta.
- Protein binding, plasma: 70% to 76%.
- Metabolism: Primarily hepatic to daunorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides.
- Half-life elimination:
  - Distribution: 2 minutes.
  - Elimination: 14-20 hours.
  - Terminal: 18.5 hours.
  - Daunorubicinol plasma half-life: 24-48 hours.
  - Excretion: Feces (~40%); urine (~25% as unchanged drug and metabolites).

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Nursing Guidelines
- Drug is a potent vesicant. Establish patency of IV before and frequently during administration as to avoid extravasation. If drug is being administered IV push administer through side port of rapidly running IV solution. If suitable vein cannot be used, central venous access may become necessary. Discuss with treating MD. If extravasation occurs treat per your institution's policy.
- Drug is not compatible with heparin. Be sure to flush heparin locked IV's or central lines before administering agent.
- Moderate to severe nausea occurs in up to 50% of patient within first 24 hours. Administer antiemetics as ordered and assess for their effectiveness.
- Inform patient about alopecia
- Potent myelosuppressive agent. Monitor CBC closely. Inform patient to report any signs or symptoms of infection, or unusual bruising or bleeding.
- Drug is cardiotoxic. Maximum lifetime dose limit is 550 mg/m^2. Monitor for signs of acute cardiac toxicity, which is possible within hours after administration. This is unrelated to cumulative dose and may manifest symptoms of pump or conduction dysfunction. Watch for signs or symptoms of CHF, pericardial effusion, and transient ECG abnormalities.
- Monitor liver function tests. Dose reduction is necessary in patients with impaired liver function.
- Radiation recall is a possibility with this drug. Monitor patient's skin at site of previous irradiation for damage.
- Inform patient that urine may be pink or red for up to 48 hours after administration.

DEXAMETHASONE (ORAL AND INTRAVENOUS ADMINISTRATION) (DXM) (NSC #34521)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for oral administration as:
- Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg.
- Solution, oral: 0.5 mg/5 mL (240 mL, 500 mL).
- Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL).

Commercially available for intravenous administration as:
- Solution, Injection, as sodium phosphate: 4 mg/mL (1 mL, 5 mL, 30 mL); 10 mg/mL (1 mL, 10 mL); [preservative free]: 10 mg/mL (1 mL).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the United States Pharmacopeia (USP)/National Formulary (NF). Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date. Store intact vials at 20°C to 25°C (68°F to 77°F). Protect from light, heat, or freezing. Diluted solutions should be used within 24 hours.

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Administration
Refer to the treatment section for specific administration instructions. Oral formulations may be taken with meals to decrease GI upset.

Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:
- Fluid and electrolyte disturbances.
- Congestive heart failure in susceptible persons.
- Hypertension.
- Psychic disturbances.
- Exacerbation or symptoms of diabetes.
- Muscle weakness.
- Osteoporosis.
- Vertebral compression fractures.
- Pancreatitis.
- Ulcerative esophagitis.
- Peptic ulcer.
- Dermatologic disturbances.
- Convulsions.
- Vertigo and headache.
- Endocrine abnormalities.
- Ophthalmic changes.
- Metabolic changes.

Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

Drug Interactions
- Cytochrome P450 Effect: Substrate of CYP3A4 (major); Induces CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong).
- Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
- Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
- Ethanol/Nutrition/Herb Interactions.
- Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
- Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
- Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

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Pharmacokinetics
- Onset of action: Prompt.
- Duration of metabolic effect: 72 hours.
- Metabolism: Hepatic.
- Half-life elimination: Normal renal function: 1.8-3.5 hours; Biological half-life: 36-54 hours.
- Time to peak, serum: Oral: 1-2 hours.
- Excretion: Urine and feces.

Nursing Guidelines
- Monitor regularly for hypertension, CHF and other evidence of fluid retention.
- Advise patient of possible mood or behavioral changes, *i.e.,* depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
- Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
- Evaluate signs of infection, particularly local candidal infections and treat appropriately.
- Monitor blood glucose frequently.
- Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.
- Advise patient that easy bruising is a side effect.

DOXORUBICIN (ADRIAMYCIN®, ADR) (NSC #123127)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation
- Commercially available for injection as:
  - Injection, powder for reconstitution: 10 mg, 50 mg.
  - Injection, solution: 2 mg/mL (5 mL, 10 mL, 25 mL, 75 mL, 100 mL).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials of solution under refrigeration and protect from light; store intact vials of lyophilized powder at room temperature. Reconstitute lyophilized powder with NS to a final concentration of 2 mg/mL. Reconstituted vials are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Infusions are stable for 48 hours at room temperature when protected from light. Solutions diluted in 50-1000 mL D5W or NS are stable for 48 hours at room temperature when protected from light. Stable with vincristine in NS for five days at room temperature protected from light.

Administration

Refer to the treatment section for specific administration instructions. Doxorubicin is administered IV push over at least 3-10 minutes, IVPB over 15-60 minutes, or continuous infusion. Doxorubicin is a potent vesicant; it is best to administer IV infusion doses through a central venous access device.

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Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

The most common side effects include:
- Dermatologic: hair loss (alopecia), darkening of your nails or separation of your nails from your nailbed.
- Gastrointestinal: nausea, vomiting, lack of appetite or increased thirst, mouth sores, stomach (abdominal) pain, diarrhea.
- Hematologic: bruise or bleed more easily.
- Cardiovascular: abnormal heart beat.
- Allergic reactions: Rash, flushed face, fever, hives, dizziness or feel faint, itching, shortness of breath or trouble breathing, swelling of your lips or tongue.
- Miscellaneous: a secondary cancer may occur when Doxorubicin is combined with other chemotherapy agents. weight changes, eye problems.

Drug Interactions
- Cytochrome P450 Effect: Substrate of CYP2D6 (major), 3A4 (major); Inhibits CYP2B6 (moderate), 2D6 (weak), 3A4 (weak).
- Increased Effect/Toxicity: Bevacizumab, trastuzumab, and cyclophosphamide may enhance the cardiotoxic effect of doxorubicin. Docetaxel and paclitaxel may enhance the adverse/toxic effect of doxorubicin; may increase the serum concentration of doxorubicin and may also increase the formation of toxic doxorubicin metabolites in heart tissue. Cyclosporine and sorafenib may increase the levels/effects of doxorubicin. CYP2D6 inhibitors may increase the levels/effects of doxorubicin. CYP3A4 inhibitors may increase the levels/effects of doxorubicin. Doxorubicin may increase the levels/effects of CYP2B6 substrates.
- Decreased Effect: Digoxin may diminish the cardiotoxic effect of doxorubicin. Doxorubicin may decrease the absorption and serum concentration of cardiac glycosides. CYP3A4 inducers may decrease the levels/effects of doxorubicin.
- Herb/Nutraceutical Interactions: Avoid St. John's wort (may decrease doxorubicin levels). Avoid black cohosh, dong quai in estrogen-dependent tumors.

Pharmacokinetics
- Distribution: Vd: 809-1214 L/m^2; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta.
- Protein binding, plasma: 70% to 76%.
- Metabolism: Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides.
- Half-life elimination:
  - Distribution: 5-10 minutes.
  - Elimination: Doxorubicin: 1-3 hours; Metabolites: 3-3.5 hours.
  - Terminal: 17-48 hours.
  - Male: 54 hours; Female: 35 hours.
- Excretion: Feces (~40% to 50% as unchanged drug); urine (~5% to 12% as unchanged drug and metabolites).
- Clearance: Male: 113 L/hour; Female: 44 L/hour.

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Nursing Guidelines
- Check CBC and platelet counts. Instruct patient to watch for signs of infection, bleeding, and anemia.
- Advise patient that their urine may turn pink in color for approximately 24 hours after administration of the drug.
- Doxorubicin is a vesicant. Check IV patency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.
- Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.
- Beware of doxorubicin (Adria) "flare" that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.
- Administer antiemetics to minimize nausea and vomiting.
- Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous Xylocaine can be used symptomatically.
- Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.
- Doxorubicin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide (Cytoxan, CTX) induced hemorrhagic cystitis.
- Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alerts to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales. Instruct patients to report any of these signs or symptoms to their health care provider.
- Document cumulative dose, which should not exceed maximum cumulative dose.
- Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.
- Drug is cardiotoxic. Maximum lifetime dose limit is 450 mg/m^2. Monitor for signs of acute cardiac toxicity, which is possible within hours after administration. This is unrelated to cumulative dose and may manifest symptoms of pump or conduction dysfunction. Watch for signs or symptoms of CHF, pericardial effusion, and transient ECG abnormalities.

MERCAPTOPURINE (PURINETHOL®) (NSC #755)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for oral administration as: Tablet: 50 mg

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (68ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF.

Administration

Refer to the treatment section for specific administration instructions. Preferably taken on an empty stomach (at least 1 hour after evening meal). 6-MP is not to be taken with milk or citrus products. Administration in children in the evening demonstrated superior outcome; administration with food did not significantly alter outcome.

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Mercaptopurine Dosing Guidelines:

60 mg/m^2 Doses of Mercaptopurine (Consolidation phase)

Body Surface Area (m²)	Daily Dose for 7 days* (1 tablet = 50 mg)
1.26 - 1.30	1½ tab / d x 6; 2 tab / d x 1
1.31 - 1.36	2 tab / d x 2; 1½ tab / d x 5
1.37 - 1.43	2 tab / d x 3; 1½ tab / d x 4
1.44 - 1.49	2 tab / d x 4; 1½ tab / d x 3
1.50 - 1.55	2 tab / d x 5; 1½ tab / d x 2
1.56 - 1.61	2 tab / d x 6; 1½ tab / d x 1
1.62 - 1.67	2 tab / d x 7
1.68 - 1.73	2 tab / d x 6; 2½ tab / d x 1
1.74 - 1.79	2½ tab / d x 2; 2 tab / d x 5
1.80 - 1.85	2½ tab / d x 3; 2 tab / d x 4
1.86 - 1.91	2½ tab / d x 4; 2 tab / d x 3
1.92 - 1.97	2½ tab / d x 5; 2 tab / d x 2
1.98 - 2.03	2½ tab / d x 6; 2 tab / d x 1

** The 7-day daily dose refers to 7-day cycles within continued daily administration (e.g., during consolidation phase and throughout maintenance). The doses should be taken in the evening, at least one hour after eating.*

75 mg/m^2 Doses of Mercaptopurine (Maintenance Phase)

Body Surface Area (m²)	Daily Dose for 7 days* (1 tablet = 50 mg)	Dose
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	(650 mg/wk)
1.30 - 1.34	2 tab / d x 6; 1½ tab / d x 1	(675 mg/wk)
1.35 - 1.39	2 tab / day	(700 mg/wk)
1.40 - 1.44	2 tab / d x 6; 2½ tab / d x 1	(725 mg/wk)
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	(750 mg/wk)
1.50 – 1.54	2 tab / d x 4; 2½ tab / d x 3	(775 mg/wk)
1.55 – 1.59	2½ tab/ d x 4; 2 tab / d x 3	(800 mg/wk)
1.60 – 1.64	2½ tab/ d x 5; 2 tab / d x 2	(825 mg/wk)
1.65 – 1.69	2½ tab/ d x 6; 2 tab / d x 1	(850 mg/wk)
1.70 – 1.74	2½ tab/ d	(875 mg/wk)
1.75 – 1.79	2½ tab/ d x 6; 3 tab / d x 1	(900 mg/wk)
1.80 – 1.84	2½ tab/ d x 5; 3 tab / d x 2	(925 mg/wk)
1.85 – 1.89	2½ tab/ d x 4; 3 tab / d x 3	(950 mg/wk)
1.90 – 1.94	3 tab/ d x 4; 2½ tab / d x 3	(975 mg/wk)
1.95 – 1.99	3 tab/ d x 5; 2½ tab / d x 2	(1000 mg/wk)

** The 7-day daily dose refers to 7-day cycles within continued daily administration (e.g., during consolidation phase and throughout maintenance). The doses should be taken in the evening, at least one hour after eating.*

Note: Thioguanine 60 mg/m^2/day PO on Days 29-42. Give thioguanine at least one hour after evening meal. 6TG is not to be taken with milk or citrus products. Adjust dose using 40 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close as possible to 420 mg/m^2.

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Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:
- Central nervous system: fever.
- Dermatologic: alopecia, hyperpigmentation, rash.
- Endocrine & metabolic: hyperuricemia.
- Gastrointestinal: anorexia, diarrhea, intestinal ulcers, pancreatitis, sprue-like symptoms, stomach pain, sore throat, nausea, vomiting.
- Genitourinary: oligospermia.
- Hematologic: myelosuppression (including anemia, granulocytopenia, leukopenia, thrombocytopenia), bleeding.
- Hepatic: hepatotoxicity, ascites, biliary stasis, hepatic damage/injury, hepatic encephalopathy, hepatic necrosis, hepatomegaly, intrahepatic cholestasis, jaundice, parenchymal cell necrosis, toxic hepatitis.
- Renal: hyperuricosuria.
- Miscellaneous: hepatosplenic T cell lymphoma, immunosuppression, infection, secondary malignancy.

Drug Interactions
- Cytochrome P450 Effect: None known.
- Increased Effect/Toxicity: Mercaptopurine may increase the levels/effects of: clozapine, leflunomide, natalizumab, vaccines (live), vitamin K antagonists. Mercaptopurine levels/toxicity may be increased by 5-ASA derivatives, allopurinol, azathioprine, denosumab, febuxostat, pimecrolimus, roflumilast, sulfamethoxazole, tacrolimus (topical), trastuzumab, trimethoprim.
- Decreased Effect: Mercaptopurine may decrease the effects/levels of BCG, coccidioidin skin test, sipuleucel-T, vaccines (inactivated), vitamin K antagonists.
- Ethanol/Nutrition/Herb Interactions:
- Food: Absorption is variable with food. Take on an empty stomach at the same time each day at least 1 hour after an evening meal. 6-MP is not to be taken with milk or citrus products.
- Herbs: Echinacea may decrease levels of mercaptopurine.

Pharmacokinetics
- Absorption: Variable and incomplete (~50%).
- Distribution: Vd: > total body water; poor CNS penetration.
- Metabolism: Hepatic and in GI mucosa; hepatically via xanthanine oxidase and methylation via TPMT to sulfate conjugates, 6-thiouric acid, and other inactive compounds; first-pass effect.
- Half-life elimination (age dependent): Children 21 minutes; Adults 47 minutes.
- Time to peak, serum: Oral: 2 hours.
- Excretion: Urine (46% as mercaptopurine and metabolites).

Nursing Guidelines
- Assess patients' concomitant medications and OTC/herbal use. Mercaptopurine can alter the efficacy/plasma levels of many medications.
- Patients should be instructed to take agent at least 1 hour after evening meal. 6-MP is not to be taken with milk or citrus products.

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- Warn patient about possible drug fever. Treat symptomatically (per protocol guidelines) and monitor for effectiveness.
- Monitor CBC w/diff. Agent is myelosuppressive with nadir at approximately 14 days. Instruct patient to report any signs or symptoms of infection or bruising/bleeding to study team.
- Monitor LFTs per protocol guidelines. Instruct patient to report abdominal pain, and/or signs of jaundice to the study team.
- Gastrointestinal side effects can be seen (i.e., anorexia, diarrhea, nausea/vomiting, etc.). Treat symptomatically and monitor for effectiveness.

METHOTREXATE (INTRAVENOUS AND ORAL) (MTX) (NSC #740)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as:
- Injection, powder for reconstitution: 1 gram.
- Injection, solution: 25 mg/mL (2 mL, 10 mL).
- Injection, solution [preservative free]: 25 mg/mL (2 mL, 4 mL, 8 mL, 10 mL, 40 mL).

Commercially available oral formulation tablets as: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature. Dilute powder with D5W or NS to a concentration of less than or equal to 25 mg/mL (20 mg and 50 mg vials) and 50 mg/mL (1 g vial). Further dilution in D5W or NS is stable for 24 hours at room temperature. Reconstituted solutions with a preservative may be stored under refrigeration for up to 3 months, and up to 4 weeks at room temperature. Store tablets at room temperature of 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Protect from light.

Administration

Refer to the treatment section for specific administration instructions. Methotrexate is usually administered slow IV push, IV Piggy Back or continuous I.V. infusion. Oral tablets may be administered with or without food.

Adverse Events

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.
Most frequently reported toxicities include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other common potential toxicities include:
- Dermatologic: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

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- Gastrointestinal: Ulcerative stomatitis, gingivitis, nausea, vomiting, diarrhea, anorexia, intestinal perforation, abdominal distress, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.
- Hematologic: Myelosuppression (including leukopenia, thrombocytopenia, anaemia, aplastic anemia, pancytopenia, neutropenia, agranulocytosis, eosinophilia), lymphadenopathy and lymphoproliferative disorders (including reversible).
- Renal: Renal failure, azotemia, cystitis, hematuria, proteinuria.
- Genital toxicity: Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia.
- Cardiovascular: Pericarditis, pericardial effusion, hypotension, thromboembolic events (arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolus).
- Central nervous system: encephalopathy, seizure, fever, chills, headache, drowsiness, speech impairment including dysarthria and aphasia, hemiparesis, paresis, cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy.
- Hepatic: Chronic cirrhosis and fibrosis, hepatotoxicity, acute hepatitis, hepatic failure.
- Neuromuscular & skeletal: stress fracture.
- Ocular: Blurred vision, transient blindness, conjunctivitis, serious visual changes.
- Respiratory: Pharyngitis, pneumonitis, respiratory fibrosis, respiratory failure, alveolitis, chronic interstitial obstructive pulmonary disease.
- Infections: infections including pneumonia, Cytomegalovirus infection, sepsis.
- Rare known potential toxicities include: nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Drug Interactions
- Metabolism/Transport Effects Substrate of P-glycoprotein, SLCO1B1
- Increased Effect/Toxicity: Methotrexate may increase the levels/effects of Cyclosporine, Leflunomide, Natalizumab, Theophylline Derivatives, Vaccines (Live), Vitamin K Antagonists.
- The levels/effects of Methotrexate may be increased by: Acitretin, Ciprofloxacin, Cyclosporine, Denosumab, Eltrombopag, Nonsteroidal Anti-Inflammatory Agents, Penicillins, P-Glycoprotein inhibitors, Pimecrolimus, Probenecid, Proton Pump Inhibitors, Salicylates, Sulfonamide Derivatives, Tacrolimus, Trastuzumab, Trimethoprim.
- Decreased Effect: Methotrexate may decrease the levels/effects of BCG, Cardiac Glycosides, Sapropterin, Sipuleucel-T, Vaccines (Inactivated), Vitamin K Antagonists.
- The levels/effects of Methotrexate may be decreased by Bile Acid Sequestrants, Echinacea, P-Glycoprotein Inducers.
- Ethanol/Nutrition/Herb Interactions:
  - Alcohol: Avoid ethanol (may be associated with increased liver injury).
  - Herb/Nutraceutical: Avoid echinacea (has immunostimulant properties).

Pharmacokinetics
- Distribution: Penetrates slowly into third space fluids (e.g., pleural effusions, ascites), exits slowly from these compartments (slower than from plasma); sustained concentrations retained in kidney and liver. Vd: 0.18 L/kg (initial); 0.4-0.8 L/kg (steady state).
- Protein binding: ~50%.

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- Metabolism: less than 10%, degraded by intestinal flora to DAMPA by Carboxypeptidase; hepatic aldehyde oxidase converts methotrexate to 7-OH methotrexate; polyglutamates are produced intracellularly and are just as potent as methotrexate; their production is dose- and duration-dependent and they are slowly eliminated by the cell once formed. Polyglutamated forms can be converted back to methotrexate.
- Half-life elimination: Low dose: 3-10 hours; High dose: 8-15 hours.
- Excretion: Urine (44% to 100%); feces (small amounts).

Nursing Guidelines
- Administer antiemetics as indicated.
- Monitor CBC. Myelosuppression is dose related and can be severe. Instruct patient to report any signs of infection, unusual bruising or bleeding to the health care team.
- Assess for mucositis (pain tenderness, redness, swelling, leukoplakia). Instruct patient in good oral care. Offer symptomatic care.
- Leucovorin rescue must be maintained. Patients who receive this in an outpatient setting must know their schedules and the importance of adherence. Monitor MTX levels after administration. Monitor renal function tests, as acute renal tubular necrosis can occur.
- Instruct patient to use sunscreening lotion or cream when exposed to the sun.
- Diarrhea is common and dose limiting, as enteritis and intestinal perforation may occur. Instruct patient to report any melena or hematemesis to the health care team immediately.
- Nausea and vomiting are uncommon with low doses, more common with high dose regimens. Premedicate with antiemetics for high dose regimens.
- Methotrexate has many drug interactions which may increase toxicity and delay clearance. Assess patient's list of medications (especially OTC) before administration. Educate patient about drug interactions.
- Pulmonary toxicity is rare and may be seen in patients with pulmonary metastasis. Assess for signs and symptoms of pulmonary dysfunction prior to and in between subsequent doses. Instruct patient to report any cough, shortness of breath, or chest pain to the health care team.
- Monitor for signs and symptoms of CNS toxicity. IT administration may increase ICP. Brain XRT followed by MTX may also cause CNS changes. Instruct patient or family member to report any of the following: dizziness, malaise, blurred vision, headache, or seizures.
- Instruct patients of the probability of infertility issues after treatment with MTX. Provide counseling and services for potential cryopreservation of sperm or eggs.

METHOTREXATE INTRATHECAL (MTX) (NSC #740)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as: Be sure to use the preservative-free formulation for intrathecal preparation:

Injection, solution [preservative-free]: 25 mg/mL (2 mL, 4 mL, 8 mL, 10 mL, 40 mL).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature. Prepare intrathecal solutions with preservative-free NS or Lactated Ringers to a final volume of up to 6 mL (volume generally based on institution or practitioner preference). Intrathecal methotrexate concentrations may be institution specific, generally

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ranging from a final concentration of 1 mg/mL up to ~2-4 mg/mL. Intrathecal dilutions are preservative-free and should be used as soon as possible after preparation. Each clinic/institution shall establish procedures to prevent errors with intrathecal administration. Intrathecal medications should NOT be prepared during the preparation of any other agents. After preparation, store intrathecal medications (until use) in an isolated location or container clearly marked with a label identifying as "intrathecal" use only.

Administration
Refer to the treatment section for specific administration instructions. Methotrexate intrathecal administration requires medication safety procedures:

- Intrathecal medication should not be prepared during the preparation of any other agents.
- After preparation, store in an isolated location or container clearly marked with a label identifying as "intrathecal" use only.
- Delivery to the patient should only be with other medications intended for administration into the central nervous system.
- Note: Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area. CSF volume correlates with age and not to BSA.

Adverse Events
Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:
- Central nervous system: Arachnoiditis, (acute reaction manifested as headache, back pain nuchal rigidity and fever).
- Subacute toxicity characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma.

Drug Interactions
Intrathecal dosing, drug interactions are not anticipated; Hold sulfamethoxazole/trimethoprim (Bactrim) on days of intrathecal administration.

Pharmacokinetics
Intrathecal dosing, no information available.

Nursing Guidelines
- Administer antiemetics as indicated.
- Monitor CBC. Myelosuppression is dose related and can be severe. Instruct patient to report any signs of infection, unusual bruising or bleeding to the health care team.
- Assess for mucositis (pain tenderness, redness, swelling, leukoplakia). Instruct patient in good oral care. Offer symptomatic care.
- Nausea and vomiting are uncommon with low doses, more common with high dose regimens. Premedicate with antiemetics for high dose regimens.
- Methotrexate has many drug interactions which may increase toxicity and delay clearance. Assess patient's list of medications (especially OTC) before administration. Educate patient about drug interactions.

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RITUXIMAB FOR CD 20-POSITIVE SUBJECTS ONLY (RITUXAN®, C2B8) (NSC #687451)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection, solution [preservative free]: 10 mg/mL (10 mL, 50 mL) [contains Polysorbate 80].

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store vials at refrigeration temperature, do not freeze or shake. Protect vials from direct sunlight. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/mL with 0.9% NaCL or D_5W. Gently invert the bag to mix the solution; do not shake. Solutions for infusion are stable at 2ºC to 8ºC for 24 hours and at room temperature for an additional 24 hours.

Administration

Do not administer I.V. push or bolus. Refer to treatment section for specific infusion instructions.

Suggested administration guidelines are (or use institutional practice):

- Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent infusions: If patient did not tolerate initial infusion follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction; increase the rate by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.

Note: If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate

Adverse Events:

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Clinically significant adverse reactions include:

- Infusion-related reactions.
- Severe mucocutaneous reactions.
- Hepatitis B reactivation with fulminant hepatitis.
- Progressive multifocal leukoencephalopathy.
- Tumor lysis syndrome.
- Infections.
- Cardiovascular adverse reactions.
- Renal toxicity.
- Bowel obstruction and perforation.

Drug Interactions

- Increased Effect/Toxicity: Monoclonal antibodies may increase the risk for allergic reactions to rituximab due to the presence of HAC antibody. Antihypertensive medications may exacerbate hypotension.
- Decreased Effect: Currently recommended not to administer live vaccines during rituximab treatment.

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- Herb/Nutraceutical Interactions: Avoid hypoglycemic herbs, including alfalfa, bilberry, bitter melon, burdock, celery, domain, fenugreek, grainier, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of rituximab).

Pharmacokinetics
- Duration: Detectable in serum 3-6 months after completion of treatment; B-cell recovery begins ~6 months following completion of treatment; median B-cell levels return to normal by 12 months following completion of treatment.
- Distribution: 4.3 L.
- Half-life elimination: Proportional to dose; wide ranges reflect variable tumor burden and changes in CD20-positive B-cell populations with repeated doses:
  - Following first dose: Mean half-life: 3.2 days.
  - Following fourth dose: Mean half-life: 8.6 days.
- Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system.

THIOGUANINE (TABLOID®) (NSC #752)

Procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation
Commercially available for oral administration as: Tablet: 40 mg (scored).

Preparation, Storage and Stability
Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 15ºC to 25ºC (59ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF.

Administration
Refer to the treatment section for specific administration instructions. Total daily dose can be given at one time.

Thioguanine Dosing Guidelines

60 mg/m² Doses of Thioguanine

Body Surface Area (m²)	Daily Dose for 7 days* (1 tablet = 40 mg)	Dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	(160 mg/wk)
1.20 - 1.24	2 tab / d x 4; 1½ tab / d x 3	(500 mg/wk)
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	(520 mg/wk)
1.30 - 1.34	2 tab / d x 6; 1½ tab / d x 1	(540 mg/wk)
1.35 - 1.39	2 tab / day	(560 mg/wk)
1.40 - 1.44	2 tab / d x 6; 2½ tab / d x 1	(580 mg/wk)
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	(600 mg/wk)
1.50 - 1.54	2 tab / d x 4; 2½ tab / d x 3	(620 mg/wk)
1.55 - 1.59	2½ tab / d x 4; 2 tab / d x 3	(640 mg/wk)
1.60 - 1.64	2½ tab / d x 5; 2 tab / d x 2	(660 mg/wk)
1.65 - 1.69	2½ tab / d x 6; 2 tab / d x 1	(680 mg/wk)
1.70 - 1.74	2½ tab / d	(700 mg/wk)

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Body Surface Area (m^2)	Daily Dose for 7 days* (1 tablet = 40 mg)	Dose
1.75 - 1.79	2½ tab / d x 6; 3 tab / d x 1	(720 mg/wk)
1.80 - 1.84	2½ tab / d x 5; 3 tab / d x 2	(740 mg/wk)
1.85 - 1.89	2½ tab / d x 4; 3 tab / d x 3	(760 mg/wk)
1.90 - 1.94	3 tab / d x 4; 2½ tab / d x 3	(780 mg/wk)
1.95 - 1.99	3 tab / d x 5; 2½ tab / d x 2	(800 mg/wk)
2.00 - 2.04	3 tab / d x 6; 2½ tab / d x 1	(820 mg/wk)

** The 7-day daily dose refers to 7-day cycles within continued daily administration during Delayed Intensification. The doses should be taken in the evening, at least one hour after eating.*

Adverse Events

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Common known potential toxicities include:

- Endocrine & metabolic: Hyperuricemia.
- Gastrointestinal: Anorexia, intestinal necrosis, intestinal perforation, nausea, stomatitis, vomiting, sore throat.
- Hematologic: Anemia (may be delayed), bleeding, pancytopenia.
- Hepatic: hepatic sinusoidal obstruction syndrome (veno-occlusive liver disease), hepatomegaly, hepatotoxicity, jaundice.
- Miscellaneous: Infection, fever.

Drug Interactions

- Cytochrome P450 Effect: None known.
- Increased Effect/Toxicity: Thioguanine may increase the effect/toxicity of clozapine, leflunomide, natalizumab, vaccines (live). The effect/toxicity of thioguanine may be increased by 5-ASA derivatives, denosumab, pimecrolimus, roflumilast, tacrolimus (topical), trastuzumab.
- Decreased Effect: Thioguanine may decrease the levels/effects of BCG, coccidioidin skin test, sipuleucel-T, vaccines (inactivated), vaccines (live).
- Ethanol/Nutrition/Herb Interactions:
  - Ethanol: Avoid ethanol as it may increase risk of hepatotoxicity.
  - Herb: Thioguanine may be decreased by Echinacea.

Pharmacokinetics

- Absorption: 14-46%, highly variable.
- Distribution: No therapeutic concentrations in the CSF.
- Metabolism: Hepatic, rapidly and extensively metabolized via thiopurine methyltransferase (TPMT) to 2-amino-6-methylthioguanine (MTG, active) and inactive compounds.
- Half-life elimination (age dependent): Children 21 minutes; Adults 47 minutes.
- Time to peak, serum: Terminal, 5-9 hours.
- Excretion: Renal 40%.

Nursing Guidelines

- Thioguanine has several drug/drug interactions. Assess patient's concomitant medications/OTC/herbal preparations closely.
- Patients should avoid alcohol while on agent as there is increased risk of hepatotoxicity.
- Total daily dose can be taken at one time. Refer to protocol for more specific administration instructions.

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- Warn patients of the risk of hyperuricemia which may result in gout like symptoms. Instruct patients to report symptoms of gout to the study team.
- GI symptoms may be seen and may be serious (*i.e.,* intestinal perforation). Treat symptomatically and monitor for effectiveness. Instruct patients to report any abdominal pain to the study team.
- Hepatotoxicity can be seen, including VOD (veno-occlusive disease). Monitor LFTs and instruct patients to report any abdominal pain or jaundice to the study team.
- Monitor CBC w/diff. Delayed and/or prolonged cytopenias can be seen. Warn patients of this possibility and instruct them to report sign/symptoms of infection and/or bruising/bleeding to the study team.

VINCRISTINE (ONCOVIN®, VCR) (NSC #67574)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available Injection, solution, as sulfate: 1 mg/mL (1 mL, 2 mL).

Preparation, Storage and Stability

Store intact vials refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light.

IV solution: Diluted in 25-50 mL NS or D5W, stable for 7 days under refrigeration, or 2 days at room temperature. In ambulatory pumps, solution is stable for 7 days at room temperature. After preparation, keep vincristine in a location away from the separate storage location recommended for intrathecal medications.

Administration

Usually administered as short 5- to 10-minute infusion (preferred); may also be administered as a slow (1 minute) push. Refer to the treatment section of the protocol for protocol specific instructions. Vincristine is a vesicant; it is best to administer IV infusion doses through a central venous access device.

Adverse Events

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

Most common known potential toxicities include:

- Dermatologic: Alopecia, rash.

Less common known potential toxicities include:

- Cardiovascular: Hypertension or hypotension.
- Central nervous system: Cranial nerve paralysis, fever, headache, motor difficulties, seizure.
- Gastrointestinal: Abdominal cramps, anorexia, constipation, diarrhea, nausea, oral ulceration, vomiting, weight loss.
- Genitourinary: Bladder atony, dysuria, polyuria, urinary retention.
- Hematologic: Myelosuppression (including leukopenia, thrombocytopenia, anaemia).
- Neuromuscular & skeletal: Cramping, jaw pain, myalgia, numbness, weakness, peripheral neuropathy manifested as loss of the deep tendon reflexes in the lower extremities, numbness, tingling, pain, paresthesia of the fingers and toes (stocking glove sensation), and "foot drop" or "wrist drop".
- Ocular: Blindness.

Rare known potential toxicities include: SIADH.

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Drug Interactions
- Cytochrome P450 Effect: Substrate of CYP3A4 (major); Inhibits CYP3A4 (weak).
- Increased Effect/Toxicity: Vincristine should be given 12-24 hours before asparaginase to minimize toxicity (may decrease the hepatic clearance of vincristine). Acute pulmonary reactions may occur with mitomycin-C. Previous or simultaneous use with mitomycin-C has resulted in acute shortness of breath and severe bronchospasm within minutes or several hours after vinca alkaloid injection and may occur up to 2 weeks after the dose of mitomycin. Itraconazole may enhance the neurotoxicity of vincristine.
- CYP3A4 inhibitors may increase the levels/effects of vincristine.
- Decreased Effect: CYP3A4 inducers may decrease the levels/effects of vincristine.
- Ethanol/Nutrition/Herb Interactions: Herb/Nutraceutical: St John's wort may decrease vincristine levels.

Pharmacokinetics
- Distribution: Vd 163-165 L/m^2; poor penetration into CSF; rapidly removed from bloodstream and tightly bound to tissues; penetrates blood-brain barrier poorly.
- Protein binding: 75%.
- Metabolism: Extensively hepatic.
- Half-life elimination: Terminal: 24 hours.
- Excretion: Feces (80%); urine (< 1% unchanged drug).

Nursing Guidelines
- Check IV patency before and frequently during administration. Vincristine is a vesicant. If extravasation occurs refer to agency extravasation policy.
- Evaluate the patient for numbness and tingling in finger tips and toes, clumsiness of hands, and difficulty walking. Instruct patient to report any of these signs or symptoms to the health care team.
- Monitor bowel function related to constipation. Encourage use of stool softeners, increased fluid and high fiber diet to avoid constipation.
- Symptoms of cranial nerve neuropathy may develop several weeks after drug administration and take 10–12 months to resolve.
- Instruct patient about potential alopecia.
- Monitor liver function tests. Dose reduction necessary in presence of elevated bilirubin.
- Myelosuppression is rare. However, monitor CBC. Instruct patient about low count precautions.
- Assess patient concomitant medication use including OTC and herbal preparations. There are many drug interactions with drugs that are either inducers or inhibitors of the CYP3A4 pathway. Patients should avoid the use of St. John's Wort, as this may decrease VCR levels.

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BLINATUMOMAB (AMG103, NSC #765986)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine antiCD19 scFv and murine anti-CD3 scFv.

Preparation, Storage and Stability

- Sites' standard procedures for preparing blinatumomab must be in compliance with the USP guidelines (ISO Class 5 or better). Use aseptic technique and prepare blinatumomab IV solution under a qualified laminar flow hood.
- Reconstitute each vial of lyophilized powder with 3 mL of preservative-free SWFI (do **not** reconstitute vials with the IV solution stabilizer); direct stream toward the side of the vial and gently swirl to avoid excess foaming. Do not shake; final reconstituted concentration is 12.5 **µg**/mL. Reconstituted solution should be clear to slightly opalescent, colorless to slightly yellow; do not use if cloudy or if precipitation occurs. **Note:** Some doses may require reconstitution of more than 1 vial of lyophilized powder.
- 24- or 48-hour infusion: Add 270 mL NS to an empty IV bag; use only polyolefin, non-DEHP PVC (non-di-ethylhexylphthalate polyvinyl chloride), or ethyl vinyl acetate (EVA) infusion bags or pump cassettes. Transfer 5.5 mL of IV solution stabilizer to the IV bag; gently mix to avoid foaming. Transfer the appropriate volume of reconstituted blinatumomab solution to the IV bag and gently mix; refer to manufacturer labeling for the specific volume of reconstituted drug to be added. Attach the IV tubing (use only polyolefin, non-DEHP PVC, or EVA tubing) to the bag with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter. Remove air from the IV bag. **Prime the IV tubing only with the prepared infusion solution**; do **not** prime with NS. If not used immediately, store at 2°C to 8°C (36°F to 46°F) for up to 8 days (infusion must be completed within this timeframe).
- 7-day infusion: Add 90 mL **bacteriostatic** NS to an empty IV bag; use only polyolefin, non-DEHP PVC, or EVA infusion bags or pump cassettes. Transfer 2.2 mL of IV solution stabilizer to the IV bag; gently mix to avoid foaming. Transfer the appropriate volume of reconstituted blinatumomab solution to the IV bag and gently mix; refer to manufacturer labeling for the specific volume of reconstituted drug to be added. Add NS to the IV bag to a final volume of 110 mL (resulting in 0.74% benzyl alcohol); gently mix (avoid foaming). Attach the IV tubing (use only polyolefin, non-DEHP PVC, or EVA tubing) to the bag; an in-line filter is not required for the 7-day infusion bag. Remove air from the IV bag. **Prime the IV tubing only with the prepared infusion solution**; do **not** prime with NS. If not used immediately, store at 2°C to 8°C (36°F to 46°F) for up to 14 days (infusion must be completed within this time frame).

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- Store intact vials (drug and solution stabilizer) in the original package at 2°C to 8°C (36°F to 46°F); protect from light. Do not freeze. Intact vials of both drug and stabilizer may be stored for up to 8 hours at room temperature. Reconstituted solution is stable for up to 4 hours at 23°C to 27°C (73°F to 81°F) or up to 24 hours at 2°C to 8°C (36°F to 46°F). Solutions diluted for infusion **(preservative free)** are stable in NS for up to 48 hours at 23°C to 27°C (73°F to 81°F) or up to 8 days at 2°C to 8°C (36°F to 46°F). Solutions diluted for infusion **(with preservative)** are stable in NS for up to 7 days at 23°C to 27°C (73°F to 81°F) or up to 14 days at 2°C to 8°C (36°F to 46°F). Infusion should be completed within these time frames; if IV bag of solution for infusion is not administered within the time frames and temperatures indicated, discard; do not refrigerate again.

Administration
- Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL:
  - For adult patients, premedicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO in each cycle.
  - For B-cell Precursor ALL patients that are not MRD-positive, premedicate with dexamethasone 20 mg intravenously within 1 hour prior to the first dose of BLINCYTO of each cycle.
- Method of Administration: Use a central line to administer the IV solution. Do not flush the IV line as it will create an IV bolus to be administered into the patient.
- 24- or 48-hour infusion: Administer 240 mL as a continuous IV infusion at a constant flow rate of 10 mL/hour for 24 hours or 5 mL/hour for 48 hours (depending on dose and concentration) through a dedicated lumen. Use a programmable, lockable, non-elastomeric infusion pump with an alarm; IV tubing should include a sterile, nonpyrogenic, low protein-binding, 0.2 micron in-line filter.
- 7-day infusion: Administer 100 mL as a continuous IV infusion at a constant flow rate of 0.6 mL/hour for 7 days through a dedicated lumen. Use a programmable, lockable, non-elastomeric infusion pump with an alarm; an in-line filter is not required for the 7-day infusion bag.
- Only use polyolefin, non-DEHP PVC, or EVA infusion bags, pump cassettes, and IV tubing. IV tubing should be primed with prepared infusion solution, not NS. Premedication is required prior to some doses (see Dosing: Adult for further details).
- Infusion bag contains overfill (to account for tubing priming volume). Do **not** flush infusion line, particularly when changing infusion bags or at completion of infusion; may result in excess dosage and complications. Do not infuse other medications through the same line.

NOTE: Infusion interruption: Record all interruptions. Technical or logistical interruption must be as minimal as possible and restart the infusion as soon as possible. If an interruption is longer than four hours, the restart of the infusion must take place in the hospital under supervision of the investigator. Monitor patients for potential adverse events as described in the protocol and the Investigator Brochure.

Drug Interactions
No formal drug interaction studies have been conducted with blinatumomab. Initiation of blinatumomab treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g. warfarin) or drug concentrations (*e.g.* cyclosporine).

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Pharmacokinetics

The PK of blinatumomab appear linear over a dose range from 5 to 90 µg/m^2/day (approximately equivalent to 9 to 162 µg/day) in adult patients. Following continuous intravenous infusion, the steady-state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 µg/day and 28 µg/day for the treatment of relapsed/refractory ALL, the mean (standard deviation [SD]) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

- Distribution: The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with continuous intravenous infusion of blinatumomab.
- Metabolism: The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways.
- Elimination: The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.
- Body Weight, Body Surface Area, Gender, and Age: Results of population PK analyses indicate that age (18 to 80 years of age), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57 m^2) do not influence the PK of blinatumomab.

Renal Impairment: No formal PK studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal impairment (creatinine clearance [CrCL] ranging from 30 to 59 mL/min, N = 21) and normal renal function (CrCL more than 90 mL/min, N = 215). However, high interpatient variability was discerned (coefficient of variation up to 95.6%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function. There is no information available in patients with severe renal impairment (CrCL less than 30 mL/min) or patients on hemodialysis.

Adverse Events:

Please refer to the FDA-approved package insert for the most current product information, preparation instructions and a comprehensive list of adverse events.

The most frequent adverse events experienced after administration of blinatumomab in patients with MRD-positive B-cell Precursor ALL and Philadelphia chromosome-negative B-cell Precursor ALL in the Consolidation Phase include:

- Neutropenia
- Leukopenia
- Thrombocytopenia
- Arrhythmia
- Pyrexia
- Chills
- Infections - pathogen unspecified
- Infusion-related reaction
- Decreased immunoglobulins
- Weight increased
- Hypertransaminasemia

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- Back pain
- Headache
- Tremor
- Aphasia
- Dizziness
- Encephalopathy
- Insomnia
- Cough
- Rash
- Hypotension
- Anemia
- Nausea
- Lymphopenia
- Diarrhea
- Musculoskeletal pain
- • Hypogammaglobulinemia

Clinically significant adverse reactions include:
- Cytokine Release Syndrome.
- Neurological Toxicities, including immune effector cell-associated neurotoxicity syndrome
- Infections.
- Tumor Lysis Syndrome.
- Neutropenia and Febrile Neutropenia.
- Effects on Ability to Drive and Use Machines.
- Elevated Liver Enzymes.
- Pancreatitis.
- Leukoencephalopathy.

Nursing Guidelines
- Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction.
- Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances.
- Patients should not drive or operate dangerous machinery while receiving blinatumomab.

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Appendix 5: Backbone Chemotherapy Agents (NIMP): Dose and Treatment Modifications

Myelosuppression

There will be no routine 6-MP dose modifications based on ANC or platelets during Consolidation or Delayed Intensification Therapy.

6-MP Dose Modifications for Myelosuppression Due to TPMT Deficiency

- Patients with 6-MP-associated myelosuppression should have their thiopurine methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-MP can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the average 6-MP dose. TPMT testing and thiopurine metabolite measurements are commercially available. Heterozygotes may need a 30%-50% dose reduction of 6-MP.

Thiopurine Pharmacology and Dosage Adjustments

6-MP and 6-TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT activity varies tremendously among patients, because of a common inherited genetic defect in TPMT. One in 300 patients is completely deficient (homozygous defective) and 10% of the population are moderately deficient in TPMT activity because they have inherited one variant (non-functional) TPMT allele (*i.e.*, heterozygotes). Patients with low TPMT form higher concentrations of thioguanine nucleotides (TGNs) and are more susceptible to acute thiopurine toxicity (primarily myelosuppression involving neutropenia, thrombocytopenia, and anemia). Patients with the complete deficiency of TPMT tolerate less than 10% of protocol standard doses of 6-MP (*i.e.*, 10 to 30 mg/m^2/day given 3 days per week).

There are now CLIA-certified tests for TPMT genotype and phenotype, and for meTIMP and TGN measurements. Only three SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide. Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments

When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed:

- For patients who have received full dose thiopurine during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict the TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status.
- TPMT genotyping will be informative in all patients, if at least one mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5-10% of mutants.
  NOTE: Genotyping can be done despite recent transfusions.

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Dose Adjustments for Patients with Unacceptable Myelosuppression

- If the patient is homozygous deficient for TPMT, the thiopurine dose should be reduced to 10-20 mg/m^2/day given 3 days per week.
- If the patient is heterozygous for TPMT and has experienced significant myelosuppression, the thiopurine dose should be reduced by 30-50%. Do not increase the dose in response to a high ANC for four weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are often not necessary.
- If the patient is homozygous wild-type (high activity) for TPMT, then discontinue cotrimoxazole and use dapsone, atovaquone or pentamidine. Should ANC fall again below 500/µL on two or more occasions, decrease dose of 6-MP or MTX by 25% on an alternating basis upon resumption of therapy.

IV MTX Dose Modifications During Interim Maintenance

- After starting Course III, if ANC < 500/µL or platelets < 50,000/µL on the day that MTX is due, hold all chemotherapy and repeat blood counts in 4 days.
  - If ANC recovers to ≥ 500/µL and platelets to ≥ 50,000/µL, give the same dose of methotrexate as previously. Also administer other systemic chemotherapy that was held.
  - If ANC is still < 500/µL or platelets still < 50,000/µL, give vincristine only and repeat counts in 7 days to begin next dose of methotrexate if counts are adequate. Do not make up missed dose of methotrexate. If count criteria are still not met, call the Study Chair. Give PEG-asparaginase on schedule.
- After starting Course III, if ANC > 750/µl and platelets > 75,000/µl, escalate MTX by 50 mg/m^2 per dose.
- If ANC < 500/µL or platelets < 50,000/µL for more than 7 days after IV MTX administration, then discontinue cotrimoxazole temporarily. If toxicity for more than 7 days recurs after the next dose, once hematologic toxicity resolves (ANC > 500/µL and platelets > 50,000/µL), then IV MTX should be given at 75% of the previous dose. If neutropenia does not recur after 2 doses of IV MTX at a reduced dose, attempt to resume therapy at previous higher IV MTX dose.
- Do not give cotrimoxazole dose on the same day as methotrexate.

Oral MTX and 6-MP Dose Modifications During Maintenance Therapy (Course V)

- If ANC is < 500/µL, then hold 6-MP and PO MTX until recovery above this level and then resume at full dose once ANC ≥ 750/µL. If ANC is < 500/µL a second time, discontinue 6-MP and PO MTX until ANC ≥ 750/µL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2- to 4-week intervals provided ANC ≥ 750/µL. Consider discontinuing cotrimoxazole and switching patient to dapsone, atovaquone, or pentamidine. If ANC < 500/µL on ≥ 2 occasions during Course V, perform thiopurine pharmacology testing (see Recommendations for Thiopurine Monitoring and Dosage Adjustments section below). Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the correct point chronologically.

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- If platelet count is < 75,000/µL, then hold 6-MP and PO MTX until recovery above this level and then resume at full dose once platelets ≥ 75,000/µL. If platelet count is < 75,000/µL a second time, discontinue 6-MP and PO MTX until platelets ≥ 75,000/µL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2- to 4-week intervals provided platelets ≥ 75,000/µL. Consider discontinuing cotrimoxazole and switching patient to dapsone, atovaquone, or pentamidine. If platelets < 75,000/µL on ≥ 2 occasions during Maintenance phase, perform thiopurine pharmacology testing (see Recommendations for Thiopurine Monitoring and Dosage Adjustments section below). Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the correct point chronologically.
- Patients experiencing myelosuppression should have their TPMT status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-MP can be reduced in patients with a TPMT defect.

Oral MTX and 6-MP Dose Escalation During Maintenance Therapy

- For ANC ≥ 1500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s), first increase the dose of either PO MTX or 6-MP by 25%. Then increase the dose of the other drug by 25%. If there is no fall in ANC after both PO MTX and 6-MP have been increased once, consider noncompliance as a possibility. Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance. **If oral MTX dose is escalated to 40 mg/m^2, contact the Study Chair before further escalation**.

Hepatic Toxicity

Elevated Bilirubin

- If total bilirubin > 3 mg/dL prior to induction therapy, start dexamethasone as planned, then give vincristine and daunorubicin after bilirubin declines to < 3 mg/dL. Contact the study Principal Investigator for additional assistance.

Vincristine Dose Reductions That Occur During all Courses

Direct Bilirubin	Dose Reduction
< 3.1 mg/dL	Full dose
3.1 - 5.0 mg/dL	50%
5.1 - 6.0 mg/dL	75%
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Daunorubicin Dose Reductions During Induction

- If direct bilirubin ≥ 3 mg/dL but < 5 mg/dL on the day treatment is due, give 50% of the prescribed or previous dose of daunorubicin. Do not make up missed doses.
- If direct bilirubin ≥ 5 mg/dL but < 7 mg/dL on the day treatment is due, give 25% of the prescribed or previous dose of daunorubicin. Do not make up missed doses.
- If direct bilirubin > 7.0 mg/dL on the day treatment is due, omit daunorubicin. Do not make up missed doses.

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Doxorubicin Dose Reductions During Delayed Intensification

- If direct bilirubin ≥ 3 mg/dL but < 5 mg/dL on the day treatment is due, give 50% of the prescribed or previous dose of doxorubicin. Do not make up missed doses.
- If direct bilirubin ≥ 5 mg/dL but < 7 mg/dL on the day treatment is due, give 25% of the prescribed or previous dose of doxorubicin. Do not make up missed doses.
- If direct bilirubin ≥ 7.0 mg/dL on the day treatment is due, omit doxorubicin. Do not make up missed doses.

Oral or IV MTX Dose Reductions During Interim Maintenance and Maintenance Therapy

- If direct bilirubin > 2.0 mg/dL, then hold IV or oral MTX. When direct bilirubin ≤ 2 mg/dL, then resume MTX at the previous dose.

Elevated ALT/AST

IV MTX Dose Modifications for Interim Maintenance

- Check ALT level immediately prior to each course of intravenous (IV) MTX. (The ALT will be elevated in 100% of patients immediately after each MTX dose.)
- For ALT < 10 x upper limit of normal (ULN) at time of treatment, continue IV MTX as scheduled.
- For ALT > 10 but < 20 x ULN, discontinue cotrimoxazole and other potential hepatotoxic drugs such as fluconazole. Administer MTX therapy as scheduled for one cycle. If ALT > 10 x ULN immediately prior to next scheduled dose, then hold MTX until ALT < 10 x ULN. Once toxicity resolves, IV MTX may be resumed at previous dose.
- For ALT > 10 but < 20 x ULN that occurs on two consecutive treatment days prior to IV MTX, discontinue cotrimoxazole and other potential hepatotoxic drugs such as fluconazole. Hold MTX therapy until ALT < 10 x normal. Once toxicity resolves to this level, IV MTX may be resumed at the previous dose.
- For ALT > 20 x ULN on day of treatment, discontinue cotrimoxazole. Hold MTX therapy until ALT < 10 x normal. Once toxicity resolves to this level, IV MTX may be resumed at the previous dose.
- For ALT > 20 x normal for > 2 weeks, evaluate AST, bilirubin, alkaline phosphatase, lipase/amylase, PT, total protein, albumin, and hepatitis A, B, C, CMV, and EBV serologies. Discontinue all hepatotoxins such as fluconazole. Consider liver biopsy before additional therapy given, and discuss with the Study Chair.

Oral MTX Dose Modifications for Interim Maintenance and Maintenance Therapy

- For increase in ALT or AST > 5 x ULN, obtain total bilirubin. Monitor ALT or AST and total bilirubin every 4 weeks during Maintenance Therapy as long as transaminases remain > 5 x ULN.
- If ALT or AST > 20 x ULN on two determinations at least one week apart or bilirubin > 2 mg/dL, hold MTX and monitor labs weekly. When ALT or AST is < 5 x ULN and direct bilirubin is within normal, then resume at the previous dose.
- Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in ALT or AST > 5 x ULN.

6- MP Dose Modifications for Consolidation and Maintenance Therapy

- For increase in ALT or AST > 5 x ULN, obtain total bilirubin. Monitor ALT or AST and total bilirubin every 4 weeks during Maintenance Therapy as long as transaminases remain > 5 x ULN.

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- If ALT or AST > 20 x ULN on two determinations at least one week apart or bilirubin > 2 mg/dL, hold 6-MP and monitor labs weekly. When ALT or AST is < 5 x ULN and direct bilirubin is within normal, then resume at the previous dose.
- Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in ALT or AST > 5 x ULN.

Gastrointestinal Toxicity

Intrathecal (IT) MTX Dose Modifications During Mucositis

The dose of IT MTX will not be reduced for systemic toxicity (myelosuppression, mucositis). For mucositis ≥ Grade 3 at the time IT MTX is given, administer a single dose of leucovorin 10 mg PO 48 hours after IT MTX in order to reduce the risk of worsening mucositis.

IV MTX Dose Modifications for Mucositis During Interim Maintenance

For ≥ Grade 3 mucositis, temporarily withhold IV MTX until resolution to < Grade 1. Once toxicity has resolved, IV MTX may be resumed at 75% of previous dose. If subsequent dose is not associated with ≥ Grade 3 mucositis, attempt to re-escalate to full dose IV MTX for next dose. Missed doses of IV MTX should not be made up. Consider supportive care with IV hydration and a low dose (5 mg) of leucovorin. Consider culturing lesions for herpes simplex if mucositis persists or occurs.

Oral MTX Dose Modifications for Mucositis During Maintenance Therapy

NOTE: Maintenance Phase is not included as part of the study treatment. Any treatment after the Delayed Intensification phase will be at the Investigator's discretion, including any treatment modifications.

- For Grade 3 mucositis, PO MTX should be given at 50% of the previous dose.
- For Grade 4 toxicity, PO MTX should be temporarily held. Once toxicity resolves, then resume PO MTX at 50% of previous dose. PO MTX should then be escalated as tolerated. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Oral MTX Dose Modifications for Diarrhea and Vomiting During Maintenance Therapy

If either severe diarrhea or vomiting develops after PO MTX administration, PO MTX should be temporarily held. After resolution of symptoms (*i.e.*, < Grade 2) for a period of one week, resume PO MTX at 50% of the previous dose. PO MTX should then be escalated as tolerated. If symptoms recur, adjust the dose to the maximum tolerated to prevent recurrent symptoms. The patient should be evaluated for infectious as well as other causes of diarrhea and vomiting.

Renal/Genitourinary Toxicity

During Consolidation Therapy

For ≥ Grade 2 creatinine, hold 6-MP until toxicity resolves to < Grade 2. Once toxicity has resolved to this level, then 6-MP may be resumed at the previous dose.

Cyclophosphamide should be held in the presence of significant hematuria (> 50 RBCs/HPF – unspun urine). Hydrate before subsequent cyclophosphamide doses until specific gravity is < 1.015 and hydrate at 125 mL/m^2/hour for 24 hours after dose, and administer MESNA (200 mg/m^2) 15 minutes before the next cyclophosphamide dose and repeat at hours 3, 6, and 9. MESNA may also be given by continuous IV per institutional guidelines.

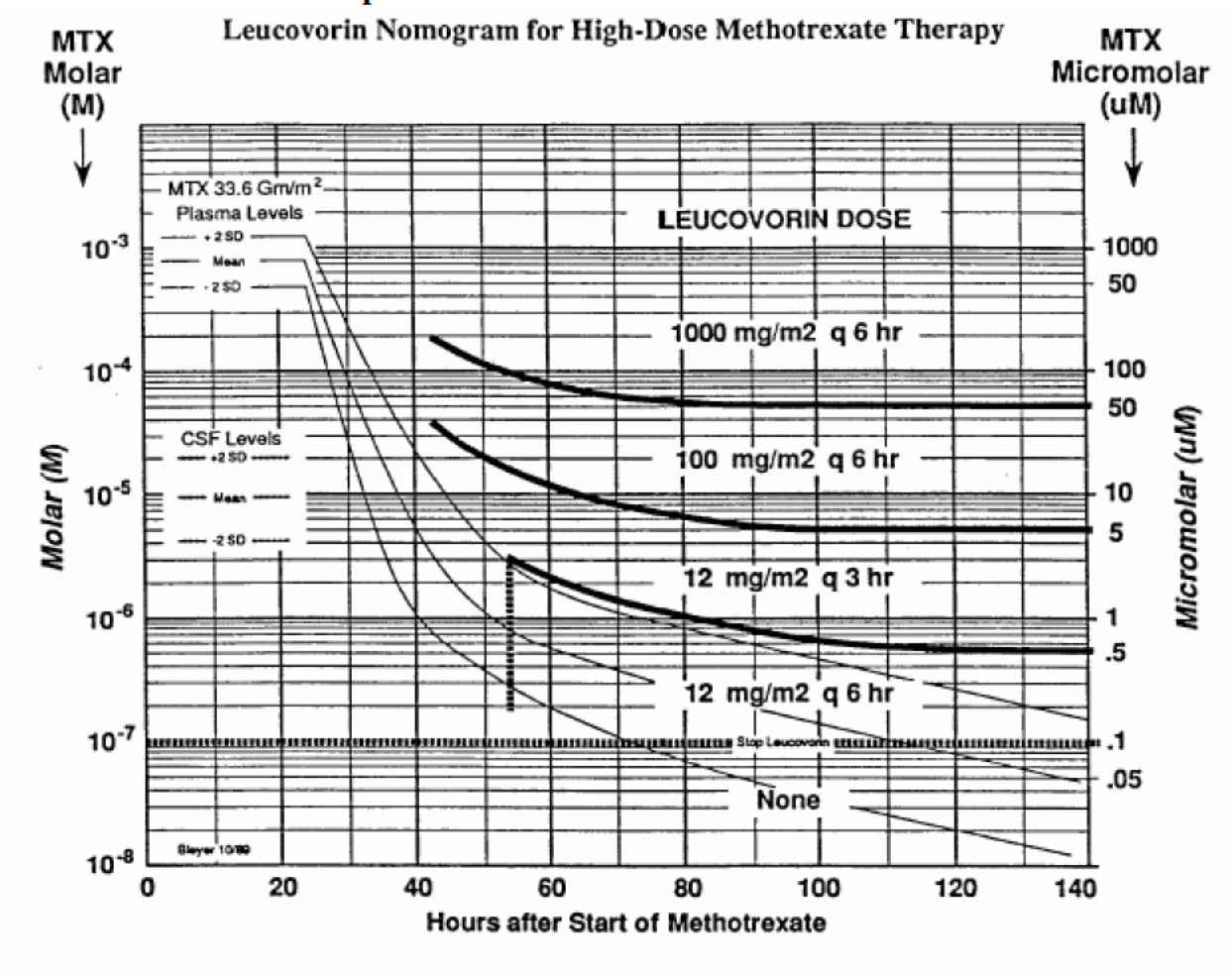
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During Interim Maintenance and Delayed Intensification Therapy

For ≥ Grade 2 creatinine or creatinine clearance < 65 mL/1.73 m^2/minute, temporarily postpone IV MTX. Hydrate vigorously. Contact the Study Principal Investigator. Resume IV MTX when creatinine falls to < Grade 1.

If a patient develops renal failure subsequent to the administration of IV MTX, obtain a serum methotrexate level and administer leucovorin according to the figure below:

Impaired Renal Methotrexate Excretion



The nomogram above should be followed unless otherwise directed by the protocol.

Leucovorin will not reverse renal toxicity but will minimize or prevent further toxicity to bone marrow and mucosal cells from prolonged MTX effect. Leucovorin should be continued until the level is < 0.1 µM. Hemodialysis is not very effective for resolving renal damage; oral charcoal, bile drainage, induced emesis, etc., have also been tried, but are not very effective. To prevent this complication, adequate fluid intake (IV or PO ≥ 3000mL/m^2) is indicated, with alkalinization (pH > 7) of urine using NaHC03. Diamox may be used to supplement NaHC03 alkalinization of the urine. Since MTX readily enters body fluids, patients with effusion(s) can have sustained high levels and must be monitored carefully.

Cyclophosphamide should be held in the presence of significant hematuria (> 50 RBCs/HPF – unspun urine). Hydrate before subsequent cyclophosphamide doses until specific gravity is < 1.015 and hydrate at 125 mL/m^2/hour for 24 hours after dose, and administer MESNA (200 mg/m^2) 15 minutes before the cyclophosphamide and repeat at hours 3, 6, and 9.

During Maintenance Therapy
NOTE: *Maintenance Phase is not included as part of the study treatment. Any treatment after the Delayed Intensification phase will be at the Investigator's discretion, including any treatment modifications.*

For ≥ Grade 2 creatinine, hold PO MTX until toxicity resolves to < Grade 2. Once toxicity has resolved to this level, then PO MTX may be resumed at the previous dose.
For ≥ Grade 2 creatinine, hold 6-MP until toxicity resolves to ≤ Grade 1. Once toxicity has resolved to this level then 6-MP may be resumed at the previous dose.

Neurologic Toxicity
Seizures
For Grade 2 seizures, hold next VCR dose. Reinstitute at previous dose at time of next planned VCR dose. For recurrent Grade 2 seizures, please contact the Study Chair.
For Grade 2 or 3 seizures, please contact the Study Chair.

Constipation or Ileus
For Grade 3 or 4 constipation or ileus, hold VCR dose, and institute aggressive hydration and laxative treatment. When toxicity resolves to ≤ Grade 1, resume VCR at 50% of previous dose at time of next scheduled dose. VCR should then be re-escalated to previous dose, as tolerated.

Pain or Motor Neuropathy from Vincristine
For Grade 3 or 4 neuropathic pain, jaw pain, vocal cord paralysis or motor neuropathy (foot drop), hold VCR. Upon resolution of toxicity to ≤ Grade 1, resume VCR at 50% of previous dose at time of next scheduled dose. If toxicity remains ≤ Grade 1, the dose of VCR may be re-escalated up to 100% of the previous dose.

Arachnoiditis
For Grade 3 or 4 arachnoiditis following IT MTX, contact the Study Chair.

Steroid Psychosis
If signs or symptoms of steroid psychosis are present, steroid treatment should be discontinued.

Methotrexate Neurotoxicity
If a patient develops neurological symptoms, including malaise, headaches, somnolence, focal neurologic deficits or seizures following administration of methotrexate, treatment with dextromethorphan may result in rapid improvement of symptoms. Prompt treatment of neurologic symptoms with 45-90 mg dextromethorphan (*e.g.*, as found in 15-30 cc Robitussin DM) every 4-6 hours x 24-48 hours should be considered. For Grade 3 or 4 neurotoxicity, hold the methotrexate and discuss the patient with the Study Chair.

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Cardiac Toxicity

Daunorubicin Dose Modifications for Induction (Course I) Therapy

In the event of congestive heart failure or SF (shortening fraction) < 29% or ejection fraction (EF) < 50%, do not administer daunorubicin.

Doxorubicin Dose Modifications for Delayed Intensification (Course IV) Therapy

In the event of congestive heart failure or SF (shortening fraction) < 29% or ejection fraction (EF) < 50%, do not administer doxorubicin. If the EF has decreased by more than 20% (absolute) from the pretreatment baseline, contact Study Chair.

Hypertension due to Dexamethasone: Do not reduce dexamethasone dose. Use sodium restriction and antihypertensive medications.

Infection or other Toxicity

Infection

Varicella Zoster: Steroids should be held during active infection, except during Remission Induction (Course I). In patients who have not had chicken pox, steroids do not need to be held during Induction Therapy.

Viral, Bacterial, or Fungal Meningitis: Omit intrathecal methotrexate until resolved.

Avascular Necrosis (AVN) (Osteonecrosis)

Contact Study Chair if AVN develops. Consider omission of further dexamethasone if AVN develops during Maintenance Therapy (Course V).

Ara-C Syndrome

For fever thought to be due to ara-C, continue the scheduled ara-C.

For ≥ Grade 3 rash, hold ara-C until rash improves ≤ Grade 2.

For conjunctival irritation, consider steroid eyedrops.

Missed doses of ara-C should be made up.

Obese Patients

With the backbone chemotherapy agents there is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012;30(13):1553-1561.

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Dose Modifications to Blinatumomab

If the interruption after an adverse reaction is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse reaction is longer than 7 days, start a new cycle.

Blinatumomab Dosage Modifications for Adverse Reactions

Adverse Reaction	Grade*	Patients Weighing ≥ 45 kg	Patients Weighing < 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	• Interrupt blinatumomab. • Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 9 µg/day, and escalate to 28 µg/day after 7 days if the adverse reaction does not recur.	• Interrupt blinatumomab. • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 5 µg/m^2/day, and escalate to 15 µg/m^2/day after 7 days if the adverse reaction does not recur.
	Grade 4	Discontinue blinatumomab permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Toxicity	Seizure	Discontinue blinatumomab permanently if more than one seizure occurs.	
	Grade 3	• Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 µg/day. • Escalate to 28 µg/day after 7 days if the adverse reaction does not recur. • If the adverse reaction occurred at 9 µg/day, or if the adverse reaction takes more than 7 days to resolve, discontinue blinatumomab permanently.	• Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 µg/m^2/day. • Escalate to 15 µg/m^2/day after 7 days if the adverse reaction does not recur. • If the adverse reaction occurred at 5 µg/m^2/day, or if the adverse reaction takes more than 7 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Discontinue blinatumomab permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	• Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 9 µg/day. Escalate to 28 µg/day after • 7 days if the adverse reaction does not recur. • If the adverse reaction takes more than 14 days to resolve, discontinue blinatumomab permanently.	• Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 5 µg/m^2/day. • Escalate to 15 µg/m^2/day after • 7 days if the adverse reaction does not recur. • If the adverse reaction takes more than 14 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Consider discontinuing blinatumomab permanently.	

*Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening

Dose Modifications to Rituximab

NOTE: Dose modification information for rituximab is not available. Please refer to the FDA-approved package insert for the most current product information. In lieu of this, the following was adapted from the **WARNINGS AND PRECAUTIONS** sections of rituximab label:

Infusion-Related Reactions
Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$).

Severe Mucocutaneous Reactions
Discontinue rituximab in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab products to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus Reactivation (HBV)
Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming rituximab treatment in patients who develop HBV reactivation. Resumption of rituximab treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive Multifocal Leukoencephalopathy (PML)
Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, includes MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for John Cunningham virus (JC virus [JCV]) DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of rituximab must be permanently discontinued.

Discontinue rituximab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Tumor Lysis Syndrome (TLS)
Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

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Infections
Discontinue rituximab for serious infections and institute appropriate anti-infective therapy. Rituximab is not recommended for use in patients with severe, active infections.

Cardiovascular Adverse Reactions
Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity
Monitor closely for signs of renal failure and discontinue rituxumab in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation
Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

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Appendix 6: Radiation Therapy and Quality Assurance

Radiation therapy will be administered based on Investigator discretion

Cranial Irradiation for CNS3 Patients

All patients who present with CNS3 leukemia at diagnosis and who achieve a CR will receive cranial radiation during the first cycle of Maintenance Therapy.

Equipment and Calibration

According to institutional procedures.

Target Volume

Target volume consists of entire brain and meninges, including frontal lobe, cribriform plate as well as posterior halves of globes of eyes, with optic disk and nerve superior to vertex and posterior to occiput. Caudal border will be below skull base at the bottom of C2 vertebral level. This will serve as the clinical target volume (CTV). The target volume shall be defined by means of CT. Care must be taken to avoid shielding the posterior orbit and cribriform plate. Slice thickness of the CT should be ≤ 3 mm

Target Dose

3D Conformal Radiation Therapy will be employed in all cases.
Dose Definition: Absorbed dose is specified in centigrays (cGy).
Tissue Heterogeneity: Corrections for tissue heterogeneity are required.
Prescribed Dose and Fractionation: A total dose of 1800 cGy will be given in 10 daily fractions of 180 cGy per fraction, administered Monday through Friday. Prescription will be to the planning target volume (PTV) that represents a 5mm expansion outside of the CTV as defined above. The lower border of the field at C2 may have the PTV expansion be relaxed to overlap with the CTV so as to place the "edge" in the interspace. It is permissible to have the PTV contour overlap with the CTV contour close to the orbit anteriorly and laterally as long as it does not compromise coverage of the intracranial space

Dose Uniformity

Dose variations in target volume will be within +7%, -5% of prescription-point dose. Field in field technique may be used to optimize dose distribution. Fluence optimization may also be employed to achieve an optimal plan.

Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For treatment interruptions greater than 7 days, notify the Principal Investigator.

Treatment Technique

Patient Position: It is recommended that the patient be treated in supine position. Appropriate immobilization should be used for day-to-day reproducibility.
Beam Configuration: Cranial volume is treated with two lateral, equally weighted photon beams. Fields will extend at least 1 cm beyond periphery of scalp.
Field Shaping: Field-shaping will be done with blocks which are at least 5 HVL thick. Multi-leaf collimators are acceptable.

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Eye Protection: Anterior compartment of the eye should be avoided where possible as long as target coverage is not compromised. Dose to the PTV should not be decreased to spare the anterior orbit. A posterior isocenter with resultant increased divergence can allow for proximal anterior compartment avoidance in some cases when more traditional approaches result in poor anterior lobe coverage. When using these measures it is important to ensure that the cribriform plate is not blocked, which will be given higher priority.

Testicular Irradiation

Patients with clinical evidence of testicular disease at diagnosis that does not resolve completely by the end of induction should receive radiation to the testes during consolidation therapy. Testicular irradiation should start during consolidation and must be completed before the end of consolidation.

Equipment and Calibration

Per institutional policies.

Target Volume

Clinical target volume consists of testes in scrotal sac. (N.B. Cremasteric reflex may move testes high up in inguinal canal.) The field may be reduced as the palpably enlarged mass decreases in size during treatment.

Target Dose

3D Conformal Radiation Therapy will be employed in all cases.
Prescription Point: The prescription point is at or near center of planning target volume (PTV) that represents a 5mm expansion outside of the CTV as defined above allowing sufficient flash.
Dose Definition: Absorbed dose is specified in centigrays (cGy).
Tissue Heterogeneity: Corrections for tissue heterogeneity are required.
Prescribed Dose and Fractionation: A total dose to prescription point will be 2400 cGy given in 12 daily fractions of 200 cGy per fraction, administered Monday through Friday.

Dose Uniformity

Dose variations in target volume will be within +7%, -5% of prescription-point dose. Uniformity requirement can be met with electron beam of appropriate energy and bolus thickness as confirmed with reviewing dosimetry on a treatment planning system, which is simplest technique. Bolus may also be needed for photon beams to fulfill dose uniformity requirement. (From International Commission on Radiation Units and Measurements [ICRU] Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity but not small low-dose volumes).

Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For treatment interruptions greater than 7 days, notify the Study Principal Investigator.

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Treatment Technique

Patient Position: It is recommended that the patient be treated in supine position. Frog-legging may be done to reduce dose to the medial thighs. Appropriate immobilization should be used for day-to-day reproducibility.

Field Shaping: Field-shaping will be done with blocks which are at least 5 half-value layer (HVL) thick. Multi-leaf collimators are acceptable. Electron set up will likely be clinical and cutouts should be used to minimize normal tissue dose while still allowing for sufficient flash.

Normal Tissue Sparing: Testes will be supported posteriorly and, if possible, extended caudally in order to minimize perineal XRT. Field will not be angled towards perineum. The penis will be excluded from field by fixing it to skin over the symphysis pubis.

Quality Assurance Documentation for Cranial and/or Testes RT

Per institutional policies

Appendix 7: Trial Conduct During National or International Public Health Emergency

It is recognized widely that the COVID -19 pandemic has impacted the conduct of clinical trials. The COVID 19 pandemic is still ongoing and may again potentially impact the conduct of clinical trials in the coming months before any preventive treatment becomes available. The impact is unknown at this point. However, challenges may arise in the next months from COVID-19 or similar disease. It may cause for example, quarantines self-imposed or institute imposed or governmental imposed, site closures, travel limitations, interruptions in the supply chain for the study drugs, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures including administering the study drug or adhering to protocol-mandated visits and laboratory/diagnostic testing.

The Sponsor is providing the following exceptional options for study related patient management in the event of disruption to the conduct of the study during the pandemic/epidemic time:

1. If scheduled visits cannot be conducted in person at the study site, it should be performed remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, patients should be interviewed to collect safety data. Patients will also be questioned regarding general health status to fulfill physical examination requirements.
2. Study drug administrations are allowed only at site according to the procedure described in the protocol. In case of any issue with study administration schedule Investigator must contact the Sponsor as indicated in Section 5.8.2.
3. Every effort should be made to adhere to protocol-specified assessments for patients on study intervention including follow-up. Safety laboratory assessment can be performed at the local laboratory near the patient, if possible.
4. Study sites should inform the Sponsor about modifications as soon as possible.
5. Missed assessment/visits should be captured as protocol deviations due to COVID-19.
6. Changes to study procedures should be documented in the source notes and in the eCRF as advised by the Sponsor. Specific information for individual patients should be captured in the eCRF that explains the basis for missing protocol-specified information in relationship to COVID-19, *i.e.*, from missed study visits or study discontinuations due to COVID-19.

I.R.I.S as the Sponsor of the study will continue to monitor the conduct and progress of the clinical study during pandemic/epidemic scenario and any changes (*e.g.*, delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and to the Health Authorities according to local guidance. Modifications made to the study conduct as a result of disruption the COVID-19 pandemic/epidemic will be summarized in the Clinical Study Report. This guidance does not supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of patients and site staff.

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Appendix 8: Instructions to Investigator for Handling Data Rights Requests

DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)–

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

- In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, *i.e.* may ask I.R.I.S.(as data controller) for:
  - Access to his/her data
  - Rectification of inaccurate/incomplete information.
  - Restriction of processing of data.
  - Objection to processing of data.
  - Data portability (receiving his/her data in a readable format).

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.
Request for exercise of rights:
Has to be a **written** one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written).
Has to be sent **by you** by e-mail or by mail **to** I.R.I.S. (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available.

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

General Data Protection Regulation (GDPR) requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a Sponsor to know the identity of the participants/volunteer participating to studies

	I.R.I.S. responsibility	**Investigator responsibility**
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	

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