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Sponsor:	NOPHO – Nordic Society of Pediatric Hematology & Oncology		
Protocol:	NOR-GRASPALL 2016		
Document Version No.:	2.0	**Document Date:**	14-May-2021

Protocol NOR-GRASPALL 2016

Single-Arm Pharmacokinetic/Pharmacodynamic and Safety Study of eryaspase (GRASPA®) for Patients with Hypersensitivity to PEG-Asparaginase, Diagnosed with Ph(-) Acute Lymphoblastic Leukemia

Protocol Number: **(Version Date)**	NOR-GRASPALL 2016 Aug 2019
Name of Test Drug:	Eryaspase
Phase:	2
Methodology:	Single arm, multi-center, multi-national study
Sponsor:	NOPHO - Nordic Society of Pediatric Hematology & Oncology Palle Juul-Jensens Boulevard 99 8200 – Aarhus N Denmark
Sponsor Representative:	Birgitte Klug Albertsen Children and Adolescent Medicine Aarhus University Hospital
Document Date:	14 MAY 2021
Document Version:	2.0

SIGNATURE PAGE

Protocol Title: **Single-Arm Pharmacokinetic/Pharmacodynamic and Safety Study of eryaspase (GRASPA®) for Patients with Hypersensitivity to PEG-Asparaginase, Diagnosed with Ph(-) Acute Lymphoblastic Leukemia**

Sponsor: NOPHO - Nordic Society of Pediatric Hematology & Oncology

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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History of revision

Version	Changes from the last version
Version 1.0	Original version
Version 2.0	Due to non-availability of data the following planned analysis has been deleted: Physical Exams, measurement of Vital Signs, performance status, efficacy exploratory analysis, and Correlating Blood Urea Nitrogen levels (BUN) at D14 with Cmax and AUC at steady state Age group has been revised to Children <18 years old and Adult ≥ 18 years old One more subgroup analysis added for Children <18: <11 years old and 11-<18 years old Summary Statistics of Antibody titre correlated with Cmax and AUC of eryapsase, has been deleted Section 6.3.1 and 6.4 has been updated

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ASN	Asparagine
ASNase	Asparaginase
ASP	Aspartate
AST	Aspartate Aminotransferase
ATIII	Antithrombin III
ATC	Anatomic Therapeutic Class
AUC	Area Under the Curve
BLQ	Below the limit of quantification
CBC	Complete blood count
CDER	The Center for Drug Evaluation and Research
CL	Clearance
eCRF	Electronic Case Report Form
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
DI	Dose Intensification
FDA	Food and Drug Administration
EFS	Event free survival

Abbreviation	Definition
EP	Evaluable patients
GCP	Good Clinical Practice
GLN	Glutamine
GLU	Glutamate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IV	Intravenous
ISF	Investigator Site File
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MeMP	Methylated metabolites
MRT	Mean Residence Time
MTX	Methotrexate
NC	Non-calculable
NOPHO	Nordic Society of Paediatric Hematology & Oncology
NS	No Sample
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol population

Abbreviation	Definition
PS	Performance status
PT	Preferred Term
PTT	Partial thromboplastin time
RBCs	Red blood cells
RFS	Relapse free survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse events
6TGN	6 Thioguanine nucleotides
Vss	Distribution Volume at steady state
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures and listings. It describes the planned analyses of the data collected during the study, including the safety and efficacy variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol, for the purpose of submission to the relevant authorities and for publication as appropriate. The results of all analyses in this SAP will be included in the Clinical Study Report (CSR).

This SAP is based on the following study documents:

- Protocol Amendment Version 1.0 dated 5th August 2019
- Electronic Case Report Form (eCRF) for the study.

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guidelines. This SAP conforms to the Cytel standard operating procedure STAT C002 Timing and Content of Statistical Analysis Plans using SAP template STAT C002 TP01 Version 2, dated 19FEB2016.

The SAP should be validated and signed before study database extract for final statistical analysis.

Specifications of outputs (TLFs shells) will be described in a separate document.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the pharmacological profile of eryaspase administered to patients with acute lymphoblastic leukemia (ALL) who experience a PEG-asparaginase hypersensitivity event during induction, consolidation or subsequent phases of the multi-agent chemotherapy according to NOPHO ALL 2008 or ALLTogether pilot protocol for the treatment of children and adult patients with ALL. As indicated in the protocol, the pharmacological profile is determined by:

- The pharmacokinetic (PK) parameters for asparaginase activity will be assessed: Cmax; Ctrough (nadir); Tmax; AUC (Area Under the Curve); T1/2 (half-life); Vss (Distribution Volume at Steady State), MRT (Mean Residence Time) and CL (Clearance).
- The pharmacodynamic (PD) parameters for cerebrospinal fluid (CSF) concentrations of asparagine, aspartate, glutamine, and glutamate will be assessed.

2.2. Secondary Objectives

The secondary objectives of this study will further evaluate the eryaspase PK profile, as well as the pharmacodynamic (PD) profile, immunogenicity, safety, tolerability, and metabolites.

2.3. Primary Endpoint

The primary endpoint is the percentage of patients with asparaginase (ASNase) activity >100 U/L at 14 days following the *first* infusion (nadir).

2.4. Secondary Endpoints

2.4.1. Pharmacokinetic Evaluation:

2.4.1.1. Key Secondary Endpoint:

- The percentage of patients with ASNase activity >100 U/L at 14 days following the *fourth* infusion of the 2-week dosing intervals.

2.4.2. Pharmacodynamic Evaluation:

- Cerebrospinal fluid (CSF) concentrations of asparagine (ASN), aspartate (ASP), glutamine (GLN), and glutamate (GLU)

2.4.3. Immunogenicity:

- Anti-asparaginase antibodies.

2.4.4. Safety and Tolerability:

- Incidence of hypersensitivity (allergic reactions and silent inactivation);
- Adverse events from start of treatment until 30 days after last administration;
- Levels of cytotoxic methotrexate (MTX polyglutamates) and 6 mercaptopurine metabolites (6 thioguanine nucleotides (6TGN) and methylated metabolites (MeMP)) and of DNA-TGN levels in circulating leukocytes.

2.5. Exploratory Endpoints

- Percentage of patients with dose-adjusted (to 100 U/kg) ASNase activity >100 U/L at 14 days following the *first* and *fourth* infusions (nadir);
- Percentage of patients with ASNase activity >400 U/L at 14 days following the *first* and *fourth* infusions (nadir);
- Clinical endpoints: complete remission rate, relapse rate, relapse-free survival (RFS), event-free survival (EFS).

3. STUDY DESIGN

3.1. Synopsis of Study Design

This is a single arm, multicenter, multinational study to assess the pharmacological activity, safety and immunogenicity of eryaspase in combination with the NOPHO ALL 2008 or ALLTogether pilot protocol chemotherapy administered as second line treatment to children or adult patients from 1 to 45 years old with ALL who experience hypersensitivity reactions (clinical allergic reaction or silent inactivation) to PEG-ASNase.

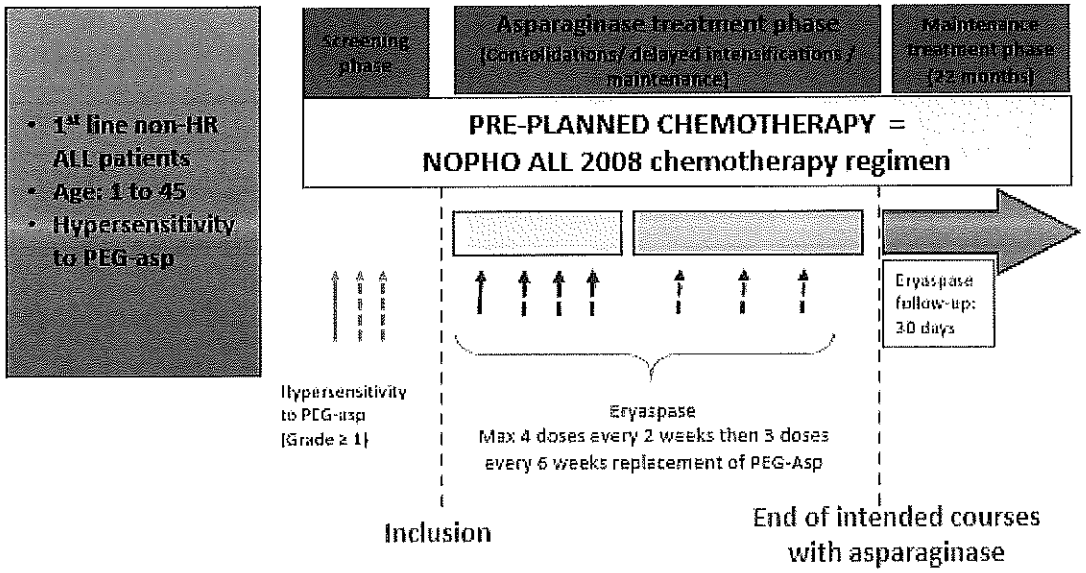
All patients will receive the NOPHO ALL 2008 or ALLTogether pilot protocol chemotherapy regimen, which consists of an induction treatment, consolidation, delayed intensification phase, maintenance phases, a CNS prophylaxis and interim maintenance for a total of 30 months' treatment duration. Once a patient presents with hypersensitivity to PEG- ASNase, eryaspase will be given as a replacement therapy for remaining scheduled PEG-ASNase administrations, Figure 1, **Figure 2.**

Eryaspase will be administered every two weeks for a maximum of four doses, and then administered every 6 weeks for three doses to the end of planned treatment according to the NOPHO ALL 2008 protocol. For patients in the ALLTogether pilot protocol, eryaspase will be administered every 2 weeks for a maximum of 7 doses. The duration of treatment with eryaspase will be dictated by the remaining number of intended courses following the occurrence of hypersensitivity to PEG-ASNase, and therefore it may range between 1-7 doses of eryaspase.

Assessments include overall safety profile of eryaspase, PK/PD parameters of eryaspase, immunogenicity of eryaspase, during successive courses of treatment with eryaspase.

Primary trial assessments for each patient will continue for one month following the end of the planned eryaspase treatment phases (approximately 6 months in case of 7 doses). Each patient will receive treatment in about 22 months after last administration of eryaspase according to the NOPHO ALL 2008 or ALLTogether pilot protocol. After cessation of therapy, patients will be followed for recurrence of disease or the development of late effects. The follow-up after cessation of therapy should be done according to guidelines on each country and site, but no assessments of those will be included for this study.

Figure 1 Study Diagram – Patients Treated According to NOPHO ALL 2008

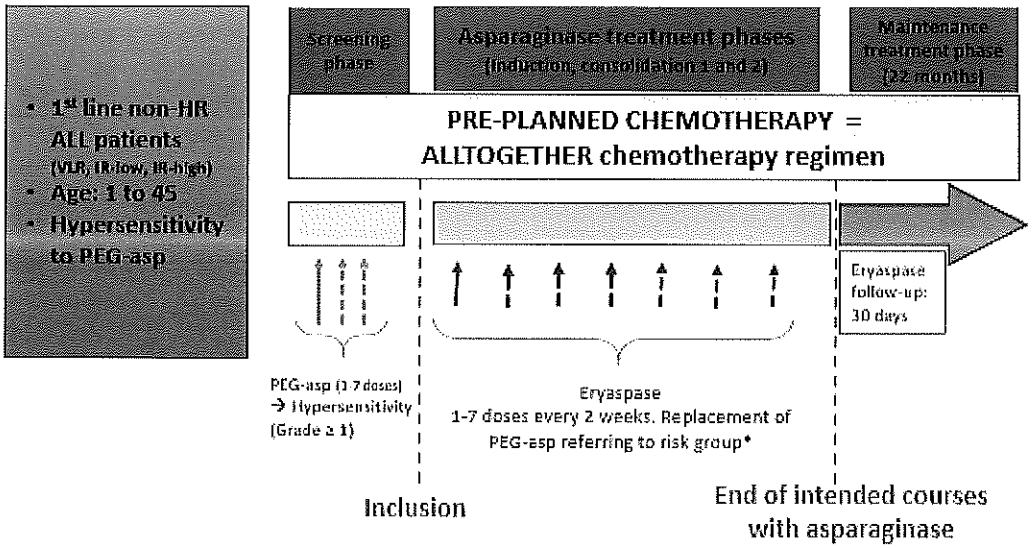


Once Eryaspase is initiated, PEG-Asparaginase regimen should be replaced by scheduled Eryaspase during all remaining chemotherapy course

Peg-Asparaginase

Eryaspase dose: 150 U/kg IV infusions will be administered every 2 weeks for maximum 4 doses then every 6 weeks for 3 doses up to the end of planned chemotherapy protocol

Figure 2 Study Diagram – Patients Treated According to NOPHO ALLTogether



Once Eryaspase is initiated, PEG-Asparaginase regimen should be replaced by scheduled Eryaspase during all remaining chemotherapy course

Peg-Asparaginase

Eryaspase dose: 150 U/kg IV infusions will be administered every 2 weeks for maximum 3-7 doses up to the end of planned chemotherapy according to protocol and risk group

*According to ALLTOGETHER protocol: VLR: 4 doses IR low: 5 doses IR high: 8 doses

3.2. Randomization Methodology

Not Applicable

3.3. Stopping Rules and Unblinding

Not Applicable

3.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Error! Reference source not found.**.

Table 1 Schedule of Assessments

			Week 1								Week 2						
Time/day	Screening	≥ 5 days (Course 1)	Baseline[a] (DAY 1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Assessment																	
Eligibility check	X[b]																
Signed written informed Consent	X[b]																
Baseline data (Demographics, medical history, ALL disease history)	X[b]																
Physical examination and vital signs incl. Karnofsky/Lansky Score	X		X														
ALL clinical assessment	X																
Pregnancy test[c]	X																
Weight		X											X				
Ordering/Quality check																	
Blood phenotyping		X[c,d]															
Prescription/ordering		X[e]											X[e]				
Irregular Antibody Screening Test		X[f] (< 72 hours)													X[f]		
Serologic crossmatch [g]			X														

Eryaspase administration				X																
Sampling																				
Amino acids sample[h,i]			X	X	X		X			X				X						
Asparaginase activity[h,j]			X1	X2	X3		X4			X5				X6						X[s]
Antibodies Titres[h,j]			X	X	X		X			X				X						X[s]
CSF amino acids[l]				(X)[k]																
Maintenance metabolites				(X)[k]																
Hematological and liver parameters[n]					(X)[m]															
Biological safety parameters[p]			X[t]																	X[ts]
Registration																				
Adverse event assessment and registration			X[q]	Ongoing registration																X[q]
Concominant treatment			X[r]	Ongoing registration																X[r]

Study Calendar, 6-Weeks Courses

			Week 1								Week 2							3	4	5	6
Time/day	Screening	≥ 5 days (COURSE 1)	Baseline[a] (DAY 1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22	29	36
Assessment																					
Eligibility check	X[b]																				
Signed written informed Consent	X[b]																				
Baseline data (Demographics, medical history,	X[b]																				

ALL disease history)																					
Physical examination and vital signs incl. Karnofsky/Lansky Score	X		X																		
ALL clinical assessment	X																				X
Pregnancy test[o]	X																				
Weight		X											X								
Ordering/Quality check																					
Blood phenotyping		X[c,d]																			
Prescription/ordering[e]		X[e]																			X[e]
Irregular Antibody Screening Test		X[f] (<72 hours)																			X[f]
Serologic crossmatch[g]			X																		
Eryaspase administration				X																	
Sampling																					
Amino acids sample[h,i]			X	X	X		X			X				X				X	X		
Asparaginase activity[h,j]			X1	X2	X 3		X4			X5				X 6				X 7	X 8		
Antibodies Titres[h,j]			X	X	X		X			X				X				X	X		
CSF amino acids[l]				(X)[k]																	
Maintenance metabolites				(X)[k]																	
Hematological and liver parameters[n]				(X)[m]																	
Biological safety parameters[p]			X[t]														X[t]		X[t]		
Registration																					
Event assessment and registration			X[q]	Ongoing registration																	X[q]
Concomitant treatment			X[r]	Ongoing registration																	X[r]

a. At the day of administration, before administration (Day 1)

b. Complete section 3 and 4 in the CRF and please send it to: Line.stensig@rm.dk
c. Complete "Blood group form" (appendix 3 in the IMP manual) and attach lab results → send to Erytech pharma: shipment@erytech.com (or *Fax*: +33 478 789 305)
d. Only before the first administration
e. Complete the "prescription form" (appendix 4 in the IMP manual) → Send the documents to Erytech Pharma at the latest 5 working days prior to each eryaspase administration: shipment@erytech.com (or *Fax*: +33 478 789 305)
f. 72-48 hours before administration → send lab results for Erytech Pharma. In case of positive results, contact Erytech pharma immediately → blood sample must be shipped to Erytech pharma/French blood bank for serologic cross match → follow guidelines in IMP manual.
g. A serologic crossmatch test between the patient's blood and the IMP is required to ensure IMP administration under safe conditions. This test can be done at the local lab or blood bank using one of the removable segment-tubes attached to the IMP bag. Complete Safety and administration form (appendix 5 in IMP manual). Erytech will now be testing blood in case of incompatibility with IMP, regardless of IAST positivity.
h. Blood sampling will be modified by local conditions and activities planned in the NOPHO ALL 2008 protocol. Aimed time slot is marked in this study calendar (1-7) and is described in the research protocol in section 8.4 and below here (#1-7) Date and time of blood sampling must be registered in the CRF. PK sample times for each course: 15 min (± 5 min) before eryaspase administration; End of infusion (0-10 min); 24 hours post-infusion (± 2 hrs); 3 days (± 1 day); 6 days (± 1 day) post-infusion; 10 days (± 2 days) post-infusion; 14 days (± 2 days) post-infusion; 21 days (± 2 days) post-infusion (6-week dose regimen only).
i. Every effort will be made to collect these samples.
j. Samples must be sent to: *Pediatric research Laboratory, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99,8200 Aarhus N, Denmark. Att. Jane Knudsen. Please notify by email before the shipment:* janeknen@rm.dk
k. When planned in NOPHO ALL 2008 protocol.
l. Must be send on dry ice to: *Pediatric research Laboratory, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99,8200 Aarhus N, Denmark. Att. Jane Knudsen. Please notify by email before the shipment:* janeknen@rm.dk. Samples can be sent at the end of study period
m. In connection with measurements of maintenance metabolites. Lab results must be attached with the CRF. Send the samples to Bonkolab, Copenhagen according to the NOPHO protocol.
n. Blood samples includes: Hematological parameters (Hemoglobin, thrombocytes, Differentiated White Blood Cell Count) and liver parameters (bilirubin, **alanine aminotransferase** (ALAT), **Lactate dehydrogenase** (LDH).
o. Serum human chorionic gonadotropin pregnancy test at screening in women of child-bearing potential and sexually active women that are of child-bearing potential is required.
p. Biological safety parameters are recommended and include: Hematological parameters (Hemoglobin, thrombocytes, Differentiated White Blood Cell Count) and liver parameters (bilirubin, **alanine aminotransferase** (ALAT), **Lactate dehydrogenase** (LDH), amylase, lipase, triglycerides and cholesterol, urinary glucose and coagulation parameters (partial thromboplastin time (PTT), prothrombin time (PT), antithrombin III and fibrinogen)
q. Be attentive to events from last course at baseline of next course. Please complete the CRF and send it after each course (Line.stensig@rm.dk). Guidelines to registration is found in the CRF.
r. Registration of other cytostatic treatment including maintenance therapy (according to the NOPHO ALL 2008 protocol) in the CRF.
s. Blood samples at day 14 coincide with baseline of next course. If applicable examinations are not needed to be repeated at both time points.
t. Additional blood counts for biological safety can be performed due to clinical conditions and as standard of care.

4. GENERAL STATISTICAL CONSIDERATIONS AND DATA HANDLING

4.1. Sample Size Justification

The trial is powered to test the hypothesis that 70% of patients meet the >100 U/L threshold compared to the null hypothesis that this threshold is achieved in 50% of patients. The null and alternative hypotheses stated here align with those outlined in previous FDA approvals, such as CDER Application (125359Orig1s000) for Erwinaze in the treatment of ALL. Based on a one-sided significance level of 2.5%, a total of 49 patients will provide 80% power for this comparison in an exact binomial test. A total of 55 patients will be recruited to allow for a ~10% dropout rate for an analysis based on evaluable patients.

Originally, the study was planned for 30 patients. An interim analysis was conducted after first 18 patients enrolled into the study, and study continued to enroll all 35 patients. The protocol was amended in August 2019 to increase the sample size up to 55 patients. The sample size increase was prompted by:

1. Continuous Erwinaze shortage and the need to complete the intended courses of asparaginase therapy
2. Encouraging safety and efficacy profile based on the informal interim analysis in the first 18 patients
3. Note that the sample size increase was not based on any evaluation of the primary endpoint from the study data collected up to that point

The primary population for analysis will be the Evaluable Patient population defined as all patients recruited into the study who provide data on whole blood ASNase activity on Day 14 (+/- 2 days) following the first administration of eryaspase.

A formal statistical hypothesis test will be performed on the primary endpoint. A single sample binomial test will be used to test the null hypothesis at the 2.5% one-sided significance level. The key secondary endpoint with the threshold of 100 U/L following the fourth infusion will be evaluated in the same way. Multiplicity will be controlled across the primary and key secondary endpoint through a pre-specified hierarchy with the primary endpoint in position 1 and the key secondary endpoint in position 2.

Descriptive statistics will be presented. For binary endpoints, 95% confidence intervals for the observed proportions will be calculated using Wilson Score method.

4.2. General Methods

The primary statistical analyses will be performed using cleaned eCRF data.

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Kaplan-Meier Methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

The following general data handling conventions, will be used in derivation of variables used in data summaries and analysis:

Term	Definition/Rule
Date of diagnosis of ALL	Date of initial ALL diagnosis
Start date of exposure period	Start date of eryaspase treatment
End date of exposure period	The end date of treatment exposure is defined as follows, depending the one occurs first: • 30 days after the last treatment administration • relapse • Death
Study Day	(date of assessment)- (date of first study drug dose) + 1
Months	Study days divided by 30.4375 days
Years	Study days divided by 365.25 days
Baseline	The latest measurement performed during screening and prior to the first dose of study drug. If the baseline value is missing, then the latest non-missing value generated prior to first dose of study drug will be used as the baseline value
Time to Event (i.e., RFS or EFS)	(date of the event) – (randomization date) + 1
Age	(date of informed consent – date of birth)/365.25 rounded down

Term	Definition/Rule
Date of diagnosis of ALL	Date of initial ALL diagnosis
Total duration of treatment	(date of last dose) – (date of first dose) + 1

4.3. Computing Environment

All statistical analyses will be performed using Statistical Analysis Systems (SAS®) release 9.2 or higher, or RStudio Version 1.2.5001, unless indicated otherwise.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. The intensity of AEs will be graded according to the NCI-CTCAE (version 5.0). Concomitant medications will be coded using World Health Organization (WHO) Drug version B3 June 2018.

4.4. Methods of Pooling Data

Not applicable to the present study.

4.5. Pharmacokinetic, pharmacodynamic, efficacy and safety variables

4.5.1. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Variables

Eryaspase PK will be evaluated using robust sampling. Blood samples for determination of whole blood asparaginase pharmacokinetics were to be collected as outlined in **Error! Reference source not found.**.

Whole blood samples will be analyzed using an enzymatic assay in which the L-AHA is hydrolyzed leading to the production of aspartic acid and hydroxylamine. Following centrifugation, the supernatant containing hydroxylamine is diluted with 8-hydroxiquinoline. The formation of indooxine after oxidation of hydroxylamine and 8-hydroxiquinoline is proportional to asparaginase activity and can be detected by absorbance reading.

Pharmacokinetic parameters to be determined include: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), trough concentration (Ctrough), elimination rate constant (λz), terminal phase half-life (t1/2), area under the concentration versus time curve (AUC), mean residence time (MRT), clearance (CL), and volume of distribution at steady state (Vss).

The pharmacodynamic effect of eryaspase on amino acid levels will be evaluated in patients, where CSF samples are collected. Reverse phase high performance liquid chromatography will be used to measure amino acids.

Immunogenicity variables include the presence of screening, confirmatory and neutralizing anti-asparaginase antibodies over time.

4.5.2. Safety Variables

Safety assessments performed during the study included clinical laboratory evaluations including hematology, serum chemistry, and monitoring of adverse events.

4.6. Analysis populations

The following patient populations will be evaluated and used for presentation and analysis of the data:

4.6.1. Evaluable Patients (EP) Population

This is the primary population for the analysis of the primary and key secondary endpoint(s), defined as all patients recruited into the study who provide data on asparaginase level on Day 14 (+/- 2 days) following the first administration of eryaspase.

The evaluation of the secondary endpoints will also be based on this population but without any imputation for missing data.

4.6.2. Per Protocol (PP) Population

All patients in the Evaluable Patients Population without major protocol deviations.

Sensitivity analyses for the primary and key secondary endpoint will be undertaken for the PP population.

Below are the examples of major protocol violations that will exclude patients from the PP population:

- No written informed consent
- No evidence of hypersensitivity reactions/silent inactivation to PEG-ASNase.
- Investigational Medicinal Product (IMP) non-safety related issues that led to delaying or skipping eryaspase dose; these include, but not limited to: RBC cross match incompatibility, IMP delivery issues, other logistical issues.

4.6.3. Safety Population

The Safety Population will consist of all patients enrolled in the study who received at least one dose of eryaspase. Safety data will be analyzed using actual dose initially received.

4.6.4. Pharmacokinetic Population

The Pharmacokinetic Population will consist of all patients with an evaluable maximum concentration (Cmax), area under the curve from time 0 to the last measurable concentration (AUC(0-t)), and Ctrough for whole blood ASNase following the first infusion. Analyses of PK data will not use any missing data imputation and will be based solely on observed data.

4.7. Adjustments for Covariates

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.8. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study given the design and objectives of this study.

4.9. Subpopulations

NA

4.10. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study will not be replaced.

4.11. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the clinical study report. General missing values and completely missing dates will not be replaced. For incomplete dates, when day and month are missing, the date will be considered as missing. When the day is the only missing date, it will be replaced by the 15th of the month of event. If there are discrepancies with the estimated date using this general rule with other available source data, then another rule will be used.

No other data imputation will be applied for missing values during the treatment phase. All available data for all patients will be presented in by-subject listings.

When deriving all other variables that use dates, for dates that include missing values, the following conventions in Table 2 will be used.

Table 2 Convention for Imputation

Value	Imputation
Missing day, month, and year	Not imputed
Missing day and month	Day imputed to June 30th
Missing day	Day imputed to the 15th

When using dates from drug administration pages for the purposes of deriving treatment exposure, the following conventions will apply:

- If the start date is missing, it will be assumed that the first drug intake was given at the date of consent/assent. This date will replace all first administration missing dates.
- If the last administration date is missing, the date will be imputed with the date taken from the "Status of the Patient at the End of the Treatment" eCRF page (Date of last treatment) or if missing, with the date of last contact taken from the "Status of the Patient" eCRF page.

4.11.1. Asparaginase Activity and Amino Acids

Missing asparaginase activity data will not be replaced or imputed.

Similar rules will be followed for calculating ASN and GLN levels.

4.11.2. Adverse Events

For missing or partial missing onset dates for adverse events, the following conventions will apply to determine whether an AE is treatment-emergent:

- If the start date of an event is completely missing, then the event is assumed to be treatment-emergent.

- If the start date has the month and year but day is missing, the event will be considered treatment-emergent if the month and year of the start date of the event are equal to, or greater than, the month and year of the date of first dose of study drug.
- If the start date has the year, but day and month are missing, the event will be considered treatment-emergent if the year of the start date of the event is to the same as, or later than, the year of the date of the first dose of study drug

4.12. Visit Windows

Specific visit windows will not be applied to this study given the variable number of courses each patient could have received. Assessments are taken at specific study days in relation to the first day of study treatment, i.e., eryaspase: Study Day 1. Patients will continue to be treated with their preplanned chemotherapy prior to inclusion into the trial.

Analyses that consider evaluations taken up to the end of the treatment with eryaspase will consider all assessments taken up to end of consolidation/intensification period, or the day before maintenance, or sooner.

4.13. Interim Analyses

An interim analysis was planned to occur once 5 patients were included. However, an interim analysis was performed following the first 18 patients enrolled into the study and was based on soft database lock. The PK and immunogenicity were evaluated in these patients, and no formal decision was taken to stop the study. Study is being continued as planned to completion. There was no stopping rule for futility built in at the interim. The study could however be stopped early for tolerability/safety concerns.

4.14. Protocol deviations

The sponsor, or designee, will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of the protocol violations, and clearly identify whether or not this violation warrants exclusion from the PP Population. This file will be finalized prior to hard database lock.

All protocol deviations will be presented in the data listings.

5. SUBJECT DISPOSITION, BASELINE DATA AND EXPOSURE SUMMARIES

5.1. Subject Disposition

Patients who give informed written consent but are not enrolled are considered screen failures. Minimal data, such as demographic information and the reason for screen failure.

A tabulation of patient disposition will be provided, including the number of screen failures, the number of patients enrolled, the number in each subject population for analysis, and the primary reasons for withdrawal from treatment and study. Disposition will also be summarized by study site. Reasons for screen failure will also be summarized.

A CONSORT diagram showing the flow of the participants through each stage of the study will be provided. A complete accounting of all patients participating in the study will be provided in overall summary table(s). This will include the final disposition of all study patients including the number of:

- Screen failures
- Patient enrolled
- Patients completed the intended courses of asparaginase therapy (both PEG-ASNase and eryaspase)
    - Completed first dose of therapy
    - Completed two doses of therapy
    - Completed 3 doses of therapy
    - Completed 4 doses of therapy
    - Completed 5 doses of therapy
    - Completed 6 doses of therapy
    - Completed 7 or more doses of therapy

- Discontinuation prior to completing planned therapy by primary reason (adverse reaction, other AEs, investigator's decision, patient's decision), relapse, death, others
- All deaths, including the follow-up period
- Deaths on study (during treatment or within 30 days of the last dose of study drug)

Distribution of patients by investigator with respect to the number of patients enrolled will be presented.

A by-subject listing of study completion information, including the reason for premature treatment and study discontinuation, if applicable, will be presented.

5.2. Demographic and Baseline Characteristics

5.2.1. Demographic Data

Demography and baseline data will be summarized using descriptive statistics.

Demographics and inclusion data on Day 1 will be analyzed on the main study analysis population. A descriptive analysis will present the following variables:

- Gender: (Male/Female), Number and % of patients
- Age (years, range, median, mean)

  Age will be calculated in years without decimal figures according to the formula: [INT (date of Visit 1 – date of birth)/365.25)], with INT (X) = whole part of X
- Age group

Classes will be defined as the followings: Children <18 years old / Adults (≥ 18 years old)

Frequency tables and/or summary tables will be provided for the following assessments:

Body Mass Index (BMI [kg/m2])

5.2.2. Disease Characteristics and ALL History

The following baseline characteristics and ALL history will be summarized for the Evaluable and PP populations, and by age class [Children <18 years old)/Adults (≥18 years old)]:

- Time since primary diagnosis of ALL, calculated in month, with 1 decimal
- Immunophenotype (B cell, T cell)
- Failure to 1st line treatment (yes/no)
- Site of disease
  - Medullary
  - Extra medullary:
    - CNS status (not done, no blast cells, Blast cells + WBC < 5 per uL, Blast cells + WBC ≥ 5 per uL)
  - Combined
- Allergic reactions to prior asparaginase treatment

- Worst Grade (Grade 1, Grade 2, Grade 3, Grade 4)
- Silent inactivation
- Combined allergic reactions and silent inactivation

- Anti-asparaginase antibody status at baseline

5.2.3. Medical History

Medical history will be coded using MedDRA dictionary, Version 21.0

The number and % of patients presenting at least with one relevant medical condition will be presented.

The relevant medical condition will be presented per System Organ Class (SOC) and Preferred Term (PT)

The number and frequency of patients presenting with at least relevant medical condition, also presented by SOC and PT. Medical history of the same nature will be pooled together, examples are presented below:

- Transaminases increased: ALT, AST and Transaminases.
- Anemia: Anemia, hemoglobin decreased.
- Thrombocytopenia: Thrombocytopenia, platelet count decreased.
- Leukopenia: Leukopenia, white blood cells count decreased.
- Leukocytosis: Leukocytosis, white blood cells count increased.
- Hyperglycemia/Diabetes: Hyperglycemia, Diabetes mellitus, Diabetes mellitus inadequate control, Type 2 diabetes mellitus, blood glucose level increased.
- Hypertriglyceridemia: Hypertriglyceridemia, triglycerides increased.
- Liver injury: Liver injury, drug-induced liver injury, hepatocellular injury, Veno-occlusive liver disease.
- Hyperuricemia: Hyperuricemia, blood uric acid increased.

In case of partial or missing end date, medical history will be assumed to be ongoing except if the partial date indicates that the condition stopped prior to the selection visit.

5.2.4. Concomitant medications:

The concomitant treatments will be coded in function of the ATC classification, using the WHO Drug dictionary, version B3 June 2018. All the treatments will be listed according to the therapeutic class.

Concomitant treatments during the study will be presented by Therapeutic Class and Preferred Term (PT) in a frequency table of the safety population.

6. STATISTICAL ANALYSIS

6.1. Analysis of the primary endpoint

The primary population for analysis will be the Evaluable Patient population defined as all patients recruited into the study who provide data on whole blood ASNase activity on Day 14 (+/- 2 days) following the first administration of eryaspase.

A formal statistical hypothesis test will be performed on the primary endpoint. A single sample binomial test will be used to test the null hypothesis at the 2.5% one-sided significance level.

Descriptive statistics will be presented. For binary endpoints, 95% confidence intervals for the observed proportions will be calculated using Wilson Score method.

6.2. Analysis of Key Pharmacokinetic Secondary Endpoints

6.2.1. Pharmacokinetic Parameter Calculations

Pharmacokinetic parameter analyses will be conducted using the Pharmacokinetic Population.

The pharmacokinetic parameters to be determined are summarized below, Table 3:

Table 3 Pharmacokinetic Parameters for Analysis

Parameter	Description
Cmax	Maximum observed concentration after each administration
tmax	Time corresponding to occurrence of Cmax
Ctrough	Observed concentration at the end of each dosing interval
t1/2	Apparent terminal elimination half-life
AUC(0-t)	AUC from time zero to the last quantifiable concentration
AUC(0-inf)	AUC from time zero extrapolated to infinity following first administration
%AUCex	Percentage of AUC(0-inf) obtained by extrapolation following first administration
MRT	Mean Residence Time
CL	Clearance following first administration
Vss	Volume of distribution following first administration

PK parameters will be calculated by non-compartmental analysis (NCA) methods from the whole blood concentration-time data using Phoenix WinNonLin version 8.0 and following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing concentration data.
- Any subjects with missing concentration data will be included in the PK analysis set provided that at least Cmax and AUC(0-t) can be reliably calculated
- All below the limit of quantification (BLQ) values pre-dose will be substituted by zeros; thereafter, BLQ values between evaluable concentrations will be set to missing
- PK parameters will be estimated according to the following:
- Cmax and Ctrough will be obtained directly from the concentration-time data.
- tmax is the time at which Cmax is observed.
- The terminal phase rate constant (λz) will be estimated by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
    - A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-Cmax data point
    - The adjusted correlation coefficient (R2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK scientist's best judgment.
- t1/2 will be calculated as ln2/λz
- AUC will be calculated using the linear trapezoidal method for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method for those arising from decreasing concentrations.
- %AUCex will be calculated as $(1 - [AUC(0\text{-}t)/AUC(0\text{-}inf)]) \times 100$.
- CL will be calculated as Dose/AUC(0-inf) following first administration.
- MRT calculated as [AUMC(0-inf) / (AUC(0-inf)]2 – TI/2 for Infusion models, where TI=infusion duration (TI may be fixed value for all subjects).
- Volume of distribution (Vss) will be calculated as MRT*CL.

Assessment of steady state will be assessed by visual inspection of the Ctrough (nadir) concentrations for the 2-week treatment regimen. As such, box and whisker plots will be generated for each nadir.

6.2.2. Pharmacokinetic Tables, Figures and Listings

Pharmacokinetic concentration data will be listed by subject including actual sampling times relative to dosing. Whole blood ASNase concentrations will be summarized by dosing course. The following descriptive statistics will be presented for concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), median, minimum and maximum values.

Pharmacokinetic parameters will be listed by subject and summarized by course following the first and fourth infusion of the 2-week regimen. Descriptive statistics for calculated PK parameters will include n, arithmetic mean, SD, CV%, geometric mean, median, minimum, and maximum values. For tmax, only median, minimum, and maximum values will be presented.

Individual whole blood concentration versus actual times will be plotted by course in linear and semi-logarithmic scale. Mean and median concentrations versus nominal times will also be presented in linear and semi-logarithmic scale by course.

All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point and will be displayed as "not calculable" or NC for the calculation of statistical summaries.

For graphs of arithmetic means and medians, all BLQ mean concentrations will be substituted by zeros. Any arithmetic mean or median that is BLQ will be excluded from log/linear presentation. Any BLQ values prior to the last quantifiable concentration will be plotted as zero for individual linear/linear graphs and excluded from log/linear graphs. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

All analyses will be based on the Pharmacokinetic Population.

6.2.3. Sensitivity, Covariate and Subgroup Analyses

The ASNase concentration on Day 14 following the first and fourth infusion for each patient will be linearly dose adjusted from 150 U/kg to 100 U/kg and the proportion of patients with values >100 U/L determined.

The primary endpoint and key secondary endpoint will be evaluated in the subgroups listed below with data presented in Forest Plots (point estimates and 95% confidence intervals) for each endpoint together with the effect in the overall evaluable patients' population. The purpose of this evaluation is to assess the homogeneity of treatment effect.

Subgroups to be used:

- Gender
- Age (<18 years, ≥18 years)
- for age <18: <11 years, 11- <18
- Antibody status at baseline (neutralizing activity as positive vs negative)
- Grade of allergic reactions to Oncaspar (Grade 1 and 2 combined vs Grade 3 and Grade 4 combined)
- Silent inactivation to Oncaspar (Yes, No)

6.3. Analysis of Secondary Pharmacodynamic Endpoints

6.3.1. Cerebrospinal Fluid Pharmacodynamics

Cerebrospinal fluid samples for ASN, GLN, ASP, and GLU will be drawn when intrathecal therapy occurs. The amino acid concentrations will be provided as follows:

- Summary statistics at various time points and presented by subject and actual sample collection time relative to eryaspase administration.
- Individual patient profile plots of amino acid levels will be presented at each time point.

6.3.2. Other Pharmacodynamic Endpoints

Levels of cytotoxic methotrexate (MTX polyglutamates) and 6-mercaptopurine metabolites (6-thioguanine nucleotides, 6TGN, and methylated metabolites, MeMP) and of DNATGN levels in circulating leukocytes will be summarized over time using descriptive statistics.

Additional exploratory analyses include:

- Correlating serum albumin levels at D14 with Cmax and AUC at steady state.

These two endpoints will be presented in a scatterplot with ASNase activity at Day 14, and Pearson's correlation coefficient will be calculated for each endpoint.

6.4. Analysis of Immunogenicity

Anti-L-ASNase antibodies will be assessed in the safety population. Results will be described by:

- Frequency tables of anti-L-ASNase antibody status (positive/negative) for Screening, Confirmatory and Neutralizing activity
- Frequency tables of antibody status at each time point of assessment.
- Summary statistics: Change in antibody status: proportion of patients with sero-conversion (negative to positive), and median time to sero-conversion

6.5. Analysis of Exploratory Endpoints

NA

7. DRUG EXPOSURE

Study duration will be derived in weeks, and defined as the number of days between the randomization and the last know study visit; i.e., (date of last visit - date of treatment +1)/7.

Analysis of all exposure to study drug will be based on the safety population. The number of doses of eryaspase planned for a respective patient depended on the phase in the treatment course to receive asparaginase. However, the overall exposure to study drug, the number of patients completing the planned doses of asparaginase, and the dose intensity will be summarized using descriptive statistics.

7.1. Dose Intensity

The dose intensity will be computed as (total actual dose received)/ (total remaining asparaginase dose expected) x 100. Visits with a non-missing planned dose and an actual dose that is zero or missing are counted as dose intensity of 0%.

7.2. Treatment Duration

Total treatment duration for eryaspase will be summarized. The duration of treatment will be defined as follows:

Eryaspase administered every 2 weeks (Day 1 and Day 15) at a dose of 150 U/kg.

Administrations will continue until the intended doses of asparaginase are completed.

Eryaspase can be reduced at the discretion of the Investigator in the event of toxicities occurring that are related to the treatment.

For eryaspase, treatment duration in months will be defined as:

(last injection date – first injection date +1) / 30.4375.

7.3. Compliance

The overall compliance (%) will be defined as: number of infusions received/number of infusions planned

Based on the definitions above, the following summary tables will be provided for eryaspase:

- Study duration (months): summary statistics,
- Treatment duration (months): summary statistics,

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- Compliance: summary statistics and frequency table for the categories <60%, 60% to <80%, 80% to 100%, >100%.

8. SAFETY AND TOLERABILITY ANALYSES

All safety summaries and analyses will be based upon the safety population, which includes all patients who received at least one dose of study drug.

The analysis of safety and tolerability data includes an overall summary of tolerability, AEs (incidence, intensity, seriousness, and relationship of AEs to the study drug), drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory results, ECG findings, and karnofsky/Lansky PS.

8.1. Adverse events

Tables summarizing the number of subjects with AEs leading to death, SAEs, or prematurely discontinued the study due to an AE, will be presented.

The primary presentation of AE data will be prepared without regard to causality or relationship to study drug. Adverse event verbatim terms are coded by the MedDRA coding system and displayed in tables and data listings using SOC and PT. The NCI CTCAE will be used to grade the severity of AEs. For AEs not included in the NCI CTCAE, categorization by mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening (Grade 4), or death (Grade 5) will be used.

AEs will be coded using the MedDRA version 21.0. In an overall AE summary table, the incidence of treatment-related TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) (in alphabetic order) for patients experiencing at least one:

- The number and percentage of patients with any treatment-emergent AE (TEAE).
- The number and percentage of patients with any TEAE assessed by the investigator as related to treatment.
- The number and percentage of patients with any treatment-emergent serious AE (SAE).
- The number and percentage of patients with any related serious TEAE.
- The number and percentage of patients with TEAEs by maximum intensity based on CTCAE grade.
- The number and percentage of patients with Grade 3 or 4 TEAE.
- The number and percentage of patients with related Grade 3 or 4 TEAE.
- The number and percentage of patients with any treatment-emergent AE by severity. The NCI CTCAE (version 5.0) will be used to grade the severity of AEs. For AEs not

included in the NCI CTCAE, categorization by mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening (Grade 4), or death (Grade 5) will be used.

- The number and percentage of patients with any treatment-emergent AE resulting in treatment discontinuation.
- The number and percentage of patients with any treatment-emergent AE with an outcome of death (fatal outcome).

In general, inferential statistical tests are not performed for AE incidence rates.

Adverse events of similar nature will be grouped together for better characterization of the adverse events, including:

- Transaminases increased: ALT increased, AST increased, and Transaminases increased.
- Anemia: Anemia, hemoglobin decreased
- Thrombocytopenia: Thrombocytopenia, platelet count decreased
- Leukopenia: Leukopenia, white blood cells count decreased
- Leukocytosis: Leukocytosis, white blood cells count increased
- Hyperglycemia/Diabetes: Hyperglycemia, Diabetes mellitus, Diabetes mellitus inadequate control, Type 2 diabetes mellitus, blood glucose level increased
- Hypertriglyceridemia: Hypertriglyceridemia, triglycerides increased
- Hepatotoxicity: Liver injury, drug-induced liver injury, hepatocellular injury, Venoocclusive liver disease
- Hyperuricemia: Hyperurecemia, blood uric acid increased
- Hypokalemia: Blood potassium decreased, hypokalemia
- Hyponatremia: Blood sodium decreased, hyponatremia
- Hypocalcemia: Blood calcium decreased, hypocalcemia
- Pancreatitis: Pancreatitis, Acute pancreatitis
- Biochemical pancreatitis: Lipase increased, Amylase increased, pancreatic enzymes increased
- Drug hypersensitivity reaction: Drug hypersensitivity, hypersensitivity, anaphylactic reaction, anaphylactic shock, erythema multiform, edema, dermatitis allergic, face edema

4. Other allergic reaction: Rash, Erythema multiform, Food allergy, Anaphylactic shock, Transfusion reactions, Angioedema, allergic transfusion reaction.

All AEs and SAEs will be collected and reported in the patient's eCRF throughout study duration (i.e. for time subject signs the informed consent and until 30 days after last administration of eryaspase or chemotherapy. All AEs along with the coded terms will be listed.

The following general rules apply to adverse events:

- TEAEs are defined as those AEs that started on or after the first dose of study medication or that worsened after the first dose of study medication and with an onset date occurring during the treatment period.
- Treatment period is defined from the first dosing day of study treatment (minimum of the first dosing day for eryaspase (Day 1) until 30 days after last dose of study treatment (maximum of the last dosing day for eryaspase). This includes the safety follow-up period as well.
- If an AE is reported for a given patient more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.
- In table summaries, patients will be counted only once at the PT level if multiple incidences of the same event occur within a SOC. Patients will be counted only once at the SOC level if multiple events occur within that SOC. For example, a patient who experiences an event of anemia and an event of neutropenia will be counted twice at the PT level (anemia, neutropenia) and once at the SOC level (vascular disorders).
- Investigator-assessed causality and relationship to study drugs will also be presented.
- In case a subject had AEs with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

8.2. Laboratory Data

Clinical laboratory values will be expressed using SI units. Local laboratories are being used for this clinical study for hematology and blood chemistry. For each individual laboratory used, laboratory reference ranges and units are collected. Reference ranges will be entered into the local laboratory normal range.

The laboratory collection CRFs (hematology and serum chemistry) include fields for additional, non-protocol-required clinically significant laboratory tests, including laboratory test name, result, units, normal range low, and normal range high.

NCI CTCAE version 5 will be used for grading applicable laboratory tests.

Standard biological assessments will be performed at the local laboratory of the Investigator's site at selection, before any eryaspase administration as follows:

- Hematology: complete blood count (CBC);
- Serum Biochemistry: lactate dehydrogenase (LDH), bilirubin, alanine aminotransferase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, potassium and calcium;
- Coagulation: fibrinogen, antithrombin III (ATIII), partial thromboplastin time (PTT), and prothrombin time.

The actual value and change from baseline on each study evaluation will be summarized for each clinical laboratory parameter. Baseline is defined as the last value taken prior to the date and time of first dose. In the event of repeat values, the last non-missing value per study day/time will be used.

Shift tables will be performed on laboratory abnormalities of the highest NCI CTCAE grade or the worst severity if there is no NCI CTCAE grade. Shifts from baseline will be classified as improved from baseline, no change from baseline, or worsened from baseline.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values. This listing will present all laboratory values for any parameter with at least one clinically significant abnormal value so that a time course for that lab parameter can be presented.

8.3. Safety Visit Compliance

To measure the impact of COVID19 on patients' visits compliance for AEs, physical exams, labs and study drug. The proportion of visits that were missed or late will be graphed over time, by calendar month. Could also have some pre/post-COVID19 subgroup analysis.

8.4. Concomitant Medications

Concomitant medications will be defined as all medications taken by the patient any time on-study (on or after the first infusion date of any of eryaspase or chemotherapy) or within 30 days after the last administration date. Previous medication will be defined as all medications taken by the patient before the first infusion of any of eryaspase or chemotherapy.

In case the date value does not allow allocation of a medication to previous or concomitant category, this medication will be considered as concomitant.

Concomitant and previous medications, not including subsequent anti-cancer therapies, will be summarized using data recorded in the "Previous and concomitant treatments" eCRF pages. Subsequent anti-cancer therapies will also be summarized separately

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and Preferred Term.

The use of concomitant medications will be included in by-subject data listing.

9. CHANGES TO PLANNED ANALYSES

The primary objectives noted in the protocol was an evaluation of the pharmacological (PK and PD) profile of eryaspase. This evaluation would be based on the PK parameters and the CSF concentration of amino acids. These two endpoints have been moved to secondary endpoints. However, the protocol does note the primary endpoint to include the percentage of patients with continuous ASNase activity >100 U/L, which is consistent with the revised primary endpoint of percentage of patients with ASNase concentration >100 U/L following the first infusion.

10. REFERENCES