STATISTICAL ANALYSIS PLAN

GRASPA-AML 2012-01

A Multicentre, open, randomized, controlled phase IIb trial evaluating efficacy and tolerability of GRASPA (L-asparaginase encapsulated in red blood cells) plus low-dose cytarabine vs low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) patients, over 65 years, unfit for intensive chemotherapy.

Protocol Number: **(Version Date)**	2012-002026-78 05Oct2015
Name of Test Drug:	GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase)
Phase:	2b
Methodology:	Open-label, Double-blind, Controlled Trial
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SIGNATURE PAGE

Protocol Title:	A Multicentre, open, randomized, controlled phase IIb trial evaluating efficacy and tolerability of GRASPA (L-asparaginase encapsulated in red blood cells) plus low-dose cytarabine vs low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) patients, over 65 years, unfit for intensive chemotherapy.
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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 guidances 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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Date: 27Nov2017

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
aPTT	Activated Partial Thromboplastin Time
ASNS	Asparagine Synthetase
ATIII	Antithrombine III
AML	Acute Myeloid Leukemia
BLLQ	Below Lower Limit of Quantification
BM	Bone Marrow
BMBC	Bone Marrow Blast Count
BMI	Body Mass Index
C	Course
CR	Complete Remission
CRi	Complete Remission with incomplete recovery
CRF	Case Report Form
CRO	Contract Research Organization
D	Day
dps	decimal places
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
HLT	High Level Terms
HLGT	High Level Group Terms
ICH	International Conference on Harmonisation
ICTA	International Clinical Trial Association
ITT	Intention To Treat
IU	International Unit
IWRS	Interactive Web Response Services
LDAC	Low dose cytarabine
LLT	Lowest Level Terms
LOCF	Last Observation Carried Forward
MEDDRA	Medical Dictionary for Regulatory Activities
mRNA	Messager Ribonucleic Acid
FAS	Full Analysis Set
FPFV	First Patient First Visit
LDAC	Low Dose Cytarabine
LPLV	Last Patient Last Visit
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PFS	Progression Free Survival
PBBC	Peripheral Blood Blast Count

Abbreviation	Definition
PP	Per Protocol
PD	Progressive Disease
PR	Partial Remission
PT	Preferred Term
QOL	Quality Of Life
RBC	Red Blood Cells
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Procedure
TFL	Tables Figures Listings
WHO	World Health Organization

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 Version 7 dated 05OCT2015
- Protocol Amendment n°4 dated 05OCT2015
- Electronic Case Report Form (eCRF) for the study.

The statistical analyses will be performed in accordance with International Conference on Harmonization (ICH) E9 guidelines. This SAP conforms to the Cytel standard operating procedure STAT C002 Timing and Content of Statistical Analysis Plans.

The SAP should be validated and signed before the study database is locked.

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

The primary analyses were to be undertaken when all enrolled patients had completed treatment and follow-up period for 2 years. However, based on the outcome of the AML Advisory Board meeting conducted on 24th January 2017, there was a consensus that the study was not adequately powered for the key endpoint of overall survival (OS) and that the purpose of the statistical analyses was therefore to identify a signal strong enough to support proceeding to phase 3.

This is a phase 2 proof of concept study and all efficacy parameters will be considered as the basis for conclusions regarding the activity of GRASPA in this population. P-values will be calculated for analyses of the primary endpoints in all patients. A two-sided 0.05 level of significance will be used as a guidance for interpretation of the data, but strict statistical significance will not be the only basis on which efficacy will be judged. In particular, the conclusions will not be based solely on the primary analysis of the primary endpoint. As indicated at the advisory board meeting, a Hazard Ratio (HR) less than 0.8 would indicate an interesting level of activity (approximately an increase in median OS from 6.4months to 8.0 months), which would warrant further investigation in a Phase 3. The activity of GRASPA will be concluded collectively in relation to the clinical relevance as indicated by the magnitude of effect across a range of endpoints (the totality of evidence).

2. OBJECTIVES OF STATISTICAL ANALYSIS

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

2.1.1. Primary objective

The primary objective is to evaluate Overall Survival (OS) in AML patients 65 to 85 years unfit for intensive chemotherapy, when treated with GRASPA plus low-dose cytarabine (LDAC) compared to low-dose cytarabine alone (LDAC).

2.1.2. Secondary and exploratory objectives

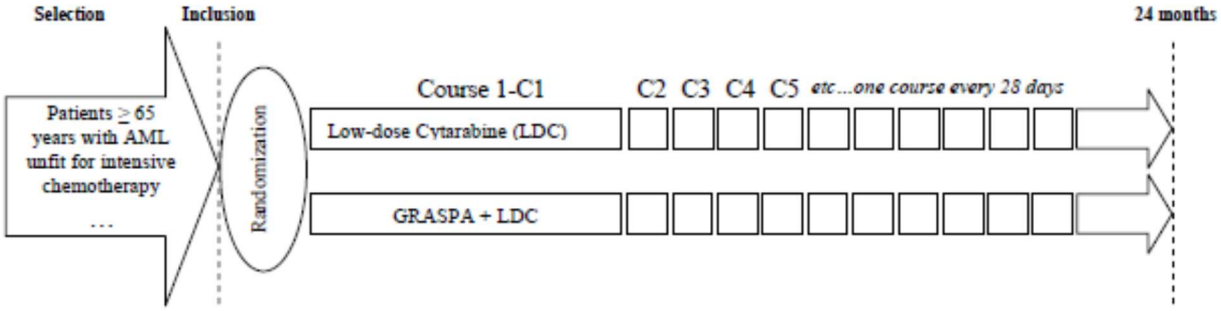
The secondary and exploratory objectives are to evaluate:

- Response to treatment
- Progression Free Survival (PFS)
- Relapse Free Survival
- Patient transfusion needs
- Patients' quality of life evolution
- Number of hospitalizations
- Safety of GRASPA in combination with cytarabine
- Pharmacokinetic and pharmacodynamic parameters of GRASPA®
- Immunogenicity of GRASPA
- Asparagine Synthetase (ASNS) expression and sensitivity to L-asparaginase in bone marrow cells (optional)
- Biomarker cytogenetic testing (optional)

3. STUDY DESIGN

3.1. Synopsis of Study Design

This is a multicentre, open label, randomized 1:2 (control versus GRASPA), controlled phase IIb trial in Europe, evaluating efficacy and tolerability of GRASPA. The trial follows the scheme below:



In both treatment and control arms, patients will be treated with subcutaneous LDAC as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days per course, each course occurring every 28 days +/- 3 days, for a duration up to 24 months. Each period of 28 days constitutes a cycle of chemotherapy. The dosage could be adjusted to 20 mg once daily in case of toxicities; a higher dose is also acceptable if required by the patient's status, at the investigator's decision.

In the experimental group, the patients will receive subcutaneous LDAC, as described above, and GRASPA (100 U/kg) given as an intravenous infusion at Day 11 of each 28 day course.

Patients will be required to attend a visit once a month, as the course begins.

When study treatment is stopped (main expected reasons are limiting toxicity, PD, or no evidence of treatment benefit), the visits will take place every 3 months until 24-months study duration has been reached.

An Independent Data Monitoring Committee (IDMC) was set-up for regular data reviews for safety: they reviewed the tolerance of GRASPA when 30 patients had been enrolled, to evaluate limiting toxicities defined as one of the following:

- grade 3 or 4 pancreatic toxicity
- grade 3 or 4 hepatic toxicity, allergic reaction, or coagulation event

- other non-hematologic grade 4 toxicity or requiring treatment change at investigator's decision

Specific attention is paid on type II diabetic patients treated with oral hypoglycemic agents for their diabetes, randomized to LDC + GRASPA.

The IDMC also reviewed safety and tolerance of GRASPA when 60 patients had been enrolled, at the end of recruitment and when 60 PFS events had been observed.

Additional information is provided in the IDMC Charter and the minutes of the IDMC meetings.

3.2. Randomization Methodology

The patients will be randomly and sequentially allocated to either one of the two treatments A or B, and the treatment allocation will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS=0 or 1 versus PS=2). This will ensure balance between the performance groups, which was been identified as a risk factor for early death.

Randomization 1:2 will be performed using Interactive Web Response Services (IWRS).

Randomization group will be confirmed to investigator by e-mail, specifying the treatment arm assigned, namely A or B, as follows:

- A: Low-dose cytarabine
- B: Low-dose cytarabine + GRASPA

Randomization will continue until 123 patients are recruited and receive study treatment.

3.3. Stopping Rules and Unblinding

An interim analysis was originally planned to be performed when half of the 123 expected PFS events had occurred (i.e. 60). The study could have been stopped at this point for futility. However, this interim analysis was not undertaken.

3.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

Table 1: Schedule of Assessments

			TREATMENT COURSE – 28 days cycle (+/- 3 days)													
Day	**D – 28 max.**	1	2	3	4	5	6	7	8	9	10	11	13	18	23	27
Visit	Inclusion	1/2/3 …														
Consent	X															
Demographics	X															
Inclusion/exclusion criteria	X															
Medical history	X															
AML history/ assessment (a)	X															X*
Clinical assessment (b)		X														
Quality of life survey		X														
Randomization	X															
Low-dose cytarabine		X	X	X	X	X	X	X	X	X	X					
GRASPA										P		X				
IAST (c)										X						
PK- PD (only for GRASPA receiving patients) (d)												X	X	X		X
Immunogenicity (only before GRASPA administration)												X				
Biology (e)	X	X (f)				X				X			X	X	X	X
Patient diary distribution and/or review		X														

(a) Bone marrow aspiration and extramedullary assessment may take place in the 4 weeks prior to randomization, for baseline status; samples for biomarkers assessments should be sent within max. 2 days after collection;

(b) including occurrence of AE/SAE; concomitant treatment;
(c) Irregular Antibodies Screening Test only for patients receiving GRASPA;
(d) See PK-PD assessments table 5
(e) hematology (CBC) ; biochemistry ; coagulation parameters; serology tests only at inclusion; pregnancy test at inclusion and end of treatment, if applicable
(f) for the first course = if biochemistry/hematology tests are available within 7 days, it is not necessary to repeat them; for coagulation tests – results should not be older than 3 days; for subsequent courses = to be performed within max. 3 days before next treatment course start;
P : prescription of GRASPA;

*: before the next treatment course

Table 2: Calendar of Study PK/PD Assessments

Table 3: Calendar of Study Assessments – Follow-Up

Visit	End of treatment	every 3 Months until M24 (M3, …)* +/- 2 weeks
AML assessment	X	X
Clinical assessment, including Adverse events review and assessment and Concomitant medications	X	X
Quality of life survey	X	X
Subsequent AML therapy	X	X
Patient diary return and review	X	

*: a phone call, at minimum, will be performed at 4 months (+/- 1 week) after end of study treatment, for safety assessment
Patient will have to attend visit every 28 days (+/- 3 days), at the start of each cycle, for a duration up to 24 months. Assessments required are provided in Tables 1 and 2.
When study treatment is stopped (see required conditions in section 8.9), the visits will take place every 3 months until 24-months study duration.

3.5. Efficacy, Pharmacokinetic, and Safety Variables

3.5.1. Efficacy Variables

The primary objective of this study is to evaluate the efficacy and tolerability of GRASPA when combined with LDAC. The primary endpoint is overall survival (OS), defined as the time elapsed between randomization and death for any cause. Patients not known to have this event are censored on the date they were last examined.

Secondary efficacy endpoints include the following:

1) Complete remission (CR), Complete remission with incomplete recovery (neutrophil or platelet regeneration, CRi), Partial remission (PR)
2) Progression-free survival (PFS) defined as the time elapsed between randomization and resistant disease or relapse or death from any cause
3) Relapse Free Survival defined only for patients who achieved CR or CRi as the time elapsed between date of CR/CRi and date of disease relapse or death from any cause
4) Percentage of patients who need transfusions (red blood cells and/or platelets), number of transfusions by patient
5) Patient quality of life evaluated using the EORTC QLQ-C30 version 3 scale
6) Number of hospitalizations (except scheduled protocol visit) required during the study

3.5.2. Pharmacokinetic Variables

Blood samples for determination of GRASPA pharmacokinetics were to be collected as outlined in the protocol. Pharmacokinetic parameters to be determined include minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), the distribution rate constant (λ_{zl}), distribution half-life (dist $t_{1/2}$), elimination rate constant (λ_{z2}), terminal elimination half-life (elim $t_{1/2}$), area under the concentration versus time curve (AUC), clearance (Cl/F), and volume of distribution (β) ($Vd_{\beta/F}$).

Pharmacokinetic and pharmacodynamic endpoints include the following:

1) Plasma concentrations of asparagine, aspartate, glutamine, glutamate
2) Whole Blood L-asparaginase activity
3) Immunogenicity by measuring titer of anti-L-asparaginase antibodies
4) Biomarker cytogenetic testing (optional)
5) Measurement of the following parameters on harvested bone marrow tumor cells (optional):
    a. Asparagine synthetase protein expression
    b. Asparagine synthetase mRNA expression

c. In vitro sensitivity to L-asparaginase

3.5.3. Safety Variables

All subjects who received at least one dose of investigational products will be included in the safety analyses. Safety data will be summarized using actual treatment received, regardless of randomized treatment.

Safety and tolerability will be assessed in terms of AEs, SAEs, laboratory data and vital signs which will be collected for all subjects. AEs will be coded according to the Medical dictionary for regulatory activities (MedDRA) version 15.1 or higher. The intensity of AEs will be graded according to the NCI-CTCAE (version 4.0).

AEs, AE leading to study treatment discontinuation, AE related to study treatment, and SAEs will be listed individually by subject, and summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment group. Summary of AEs with NCI-CTCAE grade 3 or 4 and most frequent PT will also be provided.

Specific attention will be given to NCI-CTCAE Grade 3 or 4 of pancreatic toxicity, Grade 3 or 4 of hepatotoxicity, allergic reactions or coagulation disorders, known to be potentially related to L-asparaginase as well as to hypoproteinemia and hyperglycemia/diabetes events.

Specific safety endpoints will include the following:

1) Safety of GRASPA in combination with low-dose cytarabine, with specific attention to :
    a. Grade 3 or 4 of pancreatic toxicity
    b. Grade 3 or 4 of hepatic toxicity, allergic reaction or coagulation event
    c. Grade 3 or 4 of hypoproteinemia or hyperglycemia/diabetes
    d. All other non-hematologic Grade 4 toxicities

4. SUBJECT POPULATIONS

4.1. Population Definitions

The **intent-to-treat (ITT) population** will comprise all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from protocol.

The **per-protocol (PP) population** will comprise all patients from the ITT population without any major protocol deviation that have received trial product and have completed at least one course of treatment.

All data analysed on the ITT or PP populations will be summarized using randomized treatment.

The **safety population** will comprise all patients that have received at least one administration of trial products.

All data analysed on the safety population will be summarized using actual treatment received.

The responsibility for defining the study populations and excluding patients from the analysis will be a joint decision by the sponsor, trial statistician, investigator and trial monitor. The patients to be excluded and the reasons for their exclusion must be documented and signed by those responsible prior to database release. The documentation must be stored together with the remaining trial documentation.

4.2. Protocol Violations

Major protocol violations are defined as violations liable to prevent or change the interpretation of the results of the study or may impact patient safety, affect the integrity of study data and/or affect patient's willingness to participate in the study.

The list of protocol violations will be drafted by ICTA PM and sent to sponsor for approval. The list will contain possible protocol violations (according to inclusion/exclusion criteria, disallowed treatments, minimum treatment exposure, and calendar of visits...), and significant violations which require immediate information to the Sponsor will be identified. This list may be updated in the course of the Data Management process, and will be finalized during the data review meeting before database lock.

During the data review, the impact of each violation (Minor/major) on the primary endpoint will be discussed and thus, the list of patients to be excluded from the population sets will be defined.

Patients who met protocol violation as detailed in the previous list will be listed and the number of such patient will be summarized.

5. STATISTICAL METHODS

5.1. Sample Size Justification

The sample size calculation is based on the original primary efficacy endpoint (PFS). We assumed 75% improvement in median PFS in the GRASPA plus LDAC group (treatment) compared to median PFS in the LDAC group (control). This corresponded to a median PFS of 2 months for the null hypothesis and a median of 3.5 months for the alternative hypothesis. An assumption of 24 months of accrual time and whole study duration of 48 months was used. No dropout rate was taken into consideration.

With a two-sided 5% level significance test and a power of 80%, taking into account the unbalanced group size (1 : 2), a total of 117 patients should be enrolled in order to observe 117 PFS events.

The study was designed based on the initial primary endpoint using group sequential methodology, allowing for interim analysis for futility. In order to account for this, the sample size was increased from 117 to 123 patients (41 in the LDAC group and 82 in the GRASPA plus LDAC group).

However, the sponsor amended the study, and the primary endpoint was changed from PFS to OS. It is acknowledged that the study is not powered to detect a statistically significant difference in OS; rather this is a proof of concept signal seeking study. In light of this, the one-sided significance level will be 0.025.

A decision as to whether GRASPA appears to be a promising drug in this indication will be based on the numerical values for the hazard ratio for OS. A hazard ratio of ≤ 0.80 will indicate a 20% numerical reduction in the death rate on average over time in the GRASPA group compared to control.

5.2. General Statistical Methods and Data Handling

5.2.1. General Methods

All outputs 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 with median time to event and associated 2-sided 95% confidence intervals, as well as percent of censored observations.

Formal statistical hypothesis testing to be performed on the primary efficacy endpoint will be conducted at the 1-sided, 0.025 level of significance. Secondary efficacy endpoints will be conducted at the 2-sided, 0.05 level of significance. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

Any patient not known to have had an event (death/progression) at the time of analysis will be censored based on the last recorded date on which the patient was known to be event-free.

For numeric secondary endpoints (e.g. quality of life scores) the analysis of these endpoints will be based on observed data. For repeated measures analyses using mixed models, all available data will be included in the analysis, and missing data will not be imputed.

5.2.2. Computing Environment

All statistical analyses will be performed using Statistical Analysis Systems (SAS®) release 9.2 or higher, unless indicated otherwise. All computer programs will be developed and validated according to ICTA PM (CRO) standard operating procedures.

Medical History and adverse events will be coding using MedDRA version 15.1 or higher. The intensity of AEs will be graded according to the NCI-CTCAE (version 4.0). Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, version March 2013.

5.2.3. Methods of Pooling Data

Not applicable to the present study.

5.2.4. Adjustments for Covariates

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

5.2.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a single primary efficacy endpoint.

5.2.6. Subpopulations

Analyses (estimated treatment effects and 95% confidence intervals) will be undertaken in relation to OS, PFS and objective response according to the following subgroups and presented in Forest Plots:

- Gender (male/female)
- ECOG PS (0 versus 1 versus 2)
- Age (< 70 / ≥ 70)
- Karyotype (Intermediate risk / High risk)
- Baseline bone marrow blasts, % (< 20% / ≥ 20% to ≤30%/ >30%)
- LDH levels at baseline (normal/elevated/unknown)

- FAB (French-American-British) Classification of AML (M1/2 vs. M4/5 vs. M0/6/7)

Other subgroups may be investigated in exploratory analyses.

5.2.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study were not to be replaced.

5.2.8. 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.

5.2.9. Visit Windows

Assessments are taken at specific study days in relation to the first day of LDAC (Study Day 1). LDAC is administered each day following and including Day 1, for 10 consecutive days (D1-D10). Patients in the treatment group are also administered GRASPA at Day 11. This will occur each course, which is 28 days +/- 3 days.

Biological assessments will be performed (if applicable) at D1, D5, D9, D13, D18, D23 and D27 during each course (+/- 2 days). The quality of life questionnaire and information about both hospitalizations and transfusion needs will be completed at each visit.

Follow-up visits will occur at the end of study treatment every 3 months +/- 2 weeks (i.e. M3, M6, M12,…). At minimum, a phone call will be performed every 4 months +/- 1 week after end of treatment for safety assessments.

5.3. Interim Analyses

This study was designed with a group sequential design to provide an interim analysis for futility. This futility evaluation was removed from consideration prior to its' scheduled occurrence and did not take place.

5.4. Subject Disposition

A tabulation of subject disposition will be tabulated, including the number screened, the number dosed with each treatment, the number in each subject population for analysis, the number that withdrew prior to completing the study, and reasons for withdrawal. The number in each risk group (PS=0 or 1 versus PS=2) will be tabulated.

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

5.5. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and baseline data will be provided in data listings.

5.6. Efficacy Evaluation

All efficacy analyses will be performed on the ITT population. Analyses on the primary efficacy endpoint will be repeated on the PP population.

Primary Endpoint Definition and Analysis

The primary endpoint, OS, will be defined as the time elapsed between date of randomization and date of death (or censoring) from any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

The primary objective of the trial is to estimate whether GRASPA plus LDAC is more promising than LDAC alone with respect to OS in subjects from 65 to 85 years old with newly diagnosed AML unfit for intensive chemotherapy.

Overall survival will be summarized by treatment group for the ITT population. Summaries will include the number of patients who died during the study, the number of patients who didn't die during the study (censored) with the date of censoring equal to the date that the patient was last known to be alive. Median time-to-event will be estimated from a Kaplan-Meier analysis, with associated survival curves produced. The p-value for this analysis will be provided from the stratified log-rank test, with stratification variable of type of ECOG performance status (0 or 1 versus 2) and will compare the overall survival curves between the two treatment groups. In addition, the hazard ratio and its associated 95% CI will be estimated from a stratified Cox proportional hazards model using the same strata as the Kaplan-Meier analysis (ECOG status) and censoring rules. Forest plots for the OS hazard ratios for the subgroups detailed in Section 4.2.6 will also be produced.

OS event rates at Months 12 and 24 will be summarized by treatment group for the ITT population. Summaries will include the event rate for each treatment group from the Kaplan-Meier analysis, using the estimated proportions at Month 12 and 24. A 95% CI for the difference in event rates between the treatment groups will also be provided.

5.6.1. Sensitivity Analyses for the Primary Endpoint

The analyses described in Section 4.6 will also be repeated on the PP population and separately for patients recruited before and after the protocol amendment to assess sensitivity of results to protocol compliance and amendment.

A further sensitivity analysis will be undertaken based on a stratified Cox Model, stratified for PS (0 or 1 versus 2), and including age (< 70 / ≥ 70) and Karyotype (Intermediate risk / High risk) as covariates.

5.6.2. Secondary Endpoint Definitions and Analyses

Secondary endpoints will be assessed on both the ITT and PP populations.

5.6.2.1. Complete Remission (CR), Complete Remission with Incomplete Recovery (neutrophil or platelet recovery, CRi, CRp), Partial Remission (PR)

Definitions for CR, CRi, and PR can be found in Table 4 below. This information will be collected in the section "AML-disease evaluation." Responses are entered by the site in accordance with various criteria. Exploratory analyses may include imputed responses (not site defined) based on the data available per the criteria in Table 4 for the derivation of response.

Table 4: Definitions of CR, CRi, PR, Relapse

Category	Definition according to protocol V4 to V6	Definition according to protocol V7
Morphologic leukemia-free state	Bone marrow blasts < 5% No extramedullary disease	
Complete remission (CR)	**Morphologic CR** Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/µL); platelet count > 100×10^9/L (100 000/µL); patient independent of transfusions **Cytogenetic CR** Cytogenetic normal (in those with previously abnormal cytogenetics) **Molecular CR** Molecular studies negative	
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/µL]) OR thrombocytopenia (< 100×10^9/L [100 000/µL]). patient independent of transfusions	
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25% And normalization of blood counts	
Relapse following CR	Bone marrow blasts ≥ 5%; OR reappearance of blasts in the blood OR Development of extramedullary disease	

Percentages of patients with CR, CR or Cri, and PR will be calculated and presented by treatment group. All other subjects will be considered non-responders for determining the denominator. This objective response rate data (i.e. CR, CRi or PR) will be analyzed based on a logistic regression model with both treatment and PS included in the model. The treatment effect will be summarized with an adjusted Odds Ratio (OR) and 95% confidence interval. Percentage of patients with objective response will be calculated and associated exact 95% CIs will be presented by treatment group.

5.6.2.2. Progression-Free Survival (PFS)

PFS was originally defined as death due to progression in the protocol. However, to be consistent with regulatory guidance, which considers death from any cause in its definition, this endpoint was modified to be time elapsed between randomization and disease progression or death from any cause. Patients not known to have any of these events will be censored on the date they were last known to be event-free.

Progressive disease (PD) will be defined according to the section "AML-DISEASE EVALUATION" in the e-CRF as any of the following

- At least a 25% increase of BMBC compared with baseline (defined in the section "AML history / BM evaluation at baseline", Bone Marrow Aspirate - Analyte - Blast)
- At least a 50% increase of PBBC compared with baseline
- Presence of extramedullary disease

Potential PD events presented by the patients will be reviewed and approved before database lock.

The methods for the analysis of PFS will be the same as those for OS. Specifically, PFS will be analyzed at the time of final analysis using a stratified log-rank test (stratified by PS) and displayed using Kaplan-Meier curves. Furthermore, a Cox model will also be used to test the effect of treatment and will include terms for prognostic factors (PS, age and karyoptypic group).

5.6.2.3. Relapse Free Survival (RFS)

Relapse free survival is defined for patients who have achieved CR or CRi, as time elapsed between date of CR or CRi and date of disease relapse or death from any cause. Patients not known to have any of these events will be censored on the date they were last known to be event-free.

Specifically, RFS will be analyzed at the time of final analysis using a stratified log-rank test (stratified by PS) and displayed using Kaplan-Meier curves. Furthermore, a Cox model will also be used to assess the effect of treatment and will include terms for prognostic factors (PS, age and karyotipic group). P-values for these analyses however will not be quoted as these are not randomised comparisons.

5.6.2.4. Transfusions

For collection of information regarding transfusions, the following variables will be collected at each visit:

- Transfusions (Yes/No)
  If yes,
  - mean number of transfusions
  - mean weekly number of transfusions
  - mean number of units transfused
  - at least 1 transfusion of RBC (Yes/No)

- at least 1 transfusion of platelets (Yes/No)
- at least 1 transfusion of other (Yes/No) and specifications

Any transfusion occurring after a PD will not be taken into account.

The number of transfusions will be grouped by quarter, up to an event (PD/death) and overall, by treatment group, using descriptive statistics. The mean number of transfusions of RBC and/or platelets required during the study, along with a corresponding 95% CI, will be calculated.

5.6.2.5. Quality of Life

Quality of life (QoL) will be defined by raw scores obtained from the QoL questionnaire (EORTC QLQ-C30), which is to be completed by all participants at each visit. Raw score at each visit, absolute and relative change from baseline score will be described in each treatment group for the 5 items of the functional scale, the QoL, the three symptom scales and the six single items. EORTC QoL scores will be compared across time in each treatment group using a mixed model for repeated measures data.

The event to be considered in further analyses is QoL deterioration, defined as a decrease in QoL score from baseline without any return to a better state during the study. A 10% decrease in total QoL score from baseline will be considered the primary threshold of interest. Other thresholds may be considered as exploratory analyses. Of note, death will also be considered as a QoL deterioration.

5.6.2.6. Hospitalizations

For collection of information regarding hospitalizations, the following variables will be collected at each visit:

- Hospitalization (Yes/No)
  If yes,
  - mean number of hospitalizations
  - mean weekly number of hospitalizations
  - reasons for hospitalization
  - mean duration of hospitalization (days)

The duration of hospitalization will be defined in days as the following:

- If hospitalization lasts more than 24 hours, the duration=End Date - Beginning Date + 1
- If hospitalization lasts less than 24 hours, the duration=1 day

Any hospitalization occurring after a PD will not be taken into account.

The number of hospitalizations will be grouped by quarter, up to an event (PD/death) and overall, by treatment group, using descriptive statistics. The mean number of hospitalizations occurring during the study, along with a corresponding 95% CI, will be calculated.

Additionally, a special focus will be taken on hospitalization lasting more than 24 hours, and all previous variables will be described for hospitalizations lasting more than 24 hours.

5.6.3. Exploratory Endpoints

Bone marrow biopsy/aspirate will be collected at study entry and analyzed for biomarker analysis of potentially relevant biomarkers, utilizing proteomic and transcriptomic techniques. Assessments could be repeated on further bone marrow aspirate, if possible. This data will be for exploratory purposes.

The following assays will be performed:

- Mononuclear cells from bone marrow of AML patients will be assessed for Asparagine synthetase (ASNS) expression by two different methods: real-time qRT-PCR for the quantification of ASNS mRNA and westernblot for the quantification of ASNS.
- Mutational analyses and detection of gene amplification of relevant oncogenes; e.g. *FLT3, NPM1, IDH,* or *KIT.*
- Dependent upon tissue availability, immunohistochemistry (IHC), gene expression profiling and transcriptomic profiling may be performed.
- Other biomarkers deemed relevant that may emerge with new scientific data.

Cells isolated from bone marrow by ficoll will be also cultured in presence of L-asparaginase. *In-vitro* sensitivity to L-asparaginase will be assessed at ERYTECH Pharma by measuring the cytotoxicity using a colorimetric assay.

ARN and proteic extraction obtained from samples will be frozen at ERYTECH Pharma in order to perform other analyses allowing a better knowledge of mechanism of action, or new drug development.

ASNS mRNA expression at baseline will be summarized by treatment group, and select efficacy endpoints will be plotted against ASNS mRNA expression.

5.7. Pharmacokinetic Evaluations

Pharmacokinetic, pharmacodynamic and immunogenicity parameters will only be assessed on the subgroup of subjects having received GRASPA. Samples of amino acids (asparagine, aspartate, glutamine and glutamate) and whole blood asparaginase will be taken on Days 11 and 18 of the first two cycles for all patients, on Days 11 and 18 of the remaining cycles for patients included before protocol amendment and on Days 11, 13, 18 and 27 of the first two cycles for patients included after the protocol amendment. Summary of absolute values over time and summary of change from baseline values over time will be presented separately for patients recruited before and after the protocol amendment. Prior to analysis, the concentration data will be combined with concentration data collected in previous clinical studies. The model building will be conducted using NONMEM (Icon Development Solutions, Ellicott City, MD, USA, 2009) and reported separately.

Regarding PK/PD analyses, as only 2 measurements of total blood asparaginase will be performed (D11 - 5 minutes before administration and D18), no accurate pharmacokinetic curve will be available for encapsulated asparaginase. Only those pharmacokinetic measurements which can be calculate using two timepoints will be presented.

5.8. Safety Analyses

Safety analyses will be conducted using the Safety Population.

5.8.1. Adverse Events

Safety and tolerability will be assessed in terms of AEs, SAEs, laboratory data and vital signs, which will be collected for all subjects. The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high level term (HLT), a high level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version 15.1 or higher depending on the latest version available during the study. The intensity of AEs will be graded according to the NCI-CTCAE (version 4.0).

An overview of the number of patients with AEs and the corresponding number of AEs will be presented through tables and listings:

- Total AE count
- Any AE
- Any treatment-related AE (Cytarabine and/or GRASPA®)
- Any AE of CTCAE grade ≥ 3
- Any AE of CTCAE grade = 4
- Any treatment-related (Cytarabine and/or GRASPA®) AE of CTCAE grade ≥3
- Any severe treatment-related (Cytarabine and/or GRASPA®) AE
- Any AE with outcome of death
- Any serious AE

- Any treatment-related (Cytarabine and/or GRASPA®) serious AE
- Any AE leading to permanent discontinuation
- Any treatment-related (Cytarabine and/or GRASPA®) AE leading to permanent discontinuation (Action taken=Withdrawn)
- Any AE leading to temporary discontinuation
- Any treatment-related (Cytarabine and/or GRASPA®) AE leading to temporary discontinuation (Action taken=Reduced)

An AE will be considered as "treatment-related" if the relationship to study treatment is ticked "possible," "probable" or "certain/definite".

For subject counts, subjects are included only once, even if they experienced multiple events in that category.

All the following summaries will be displayed by treatment groups on the safety population:

- All AE by System Organ Class (SOC) term, Preferred Term (PT)
- AE Experienced by ≥5% of Subjects by SOC term and PT
- Treatment-related (Cytarabine and/or GRASPA®) AE by SOC term and PT
- AE of CTCAE grade ≥ 3 by SOC term and PT
- AE of CTCAE grade = 4 by SOC term and PT
- Treatment-related (Cytarabine and/or GRASPA®) AE of CTCAE grade ≥3 by SOC term and PT
- Severe treatment-related (Cytarabine and/or GRASPA®) AE by SOC term and PT
- AE with outcome of death
- Serious AE
- Treatment-related (Cytarabine and/or GRASPA®) serious AE
- AE leading to permanent discontinuation
- AE leading to temporary discontinuation

Serious AE, AE with outcome of death and AE leading to permanent or temporary discontinuation will also be described on an individual basis: treatment group, patient's code, sex and age, investigator's reported term, preferred term, date of onset, NCI-CTCAE Criteria Grading, intensity, outcome, seriousness, suspected relationship regarding Cytarabine and GRASPA®, action taken, corrective therapy.

A special focus will be put on diabetogenic and pancreatic adverse events based on the following table:

	GRASPA + LDAC n(%)	LDAC n(%)	Total n(%)
Number of patients with xxx adverse events	**xx (x.x%)**	**xx (x.x%)**	**xx (x.x%)**
PT1	x (x.x%)	x (x.x%)	x (x.x%)
PT2	x (x.x%)	x (x.x%)	x (x.x%)
Number of events	**xx**	**xx**	**xx**
Events characteristics, n			
Serious	x (x.x%)	x (x.x%)	x (x.x%)
Cytarabine-related	x (x.x%)	x (x.x%)	x (x.x%)
GRASPA®-related	x (x.x%)	x (x.x%)	x (x.x%)
Permanent discontinuation of Cytarabine	x (x.x%)	x (x.x%)	x (x.x%)
Permanent discontinuation of GRASPA	x (x.x%)	x (x.x%)	x (x.x%)
Fatal	x (x.x%)	x (x.x%)	x (x.x%)
Number of occurences, n			
One	x (x.x%)	x (x.x%)	x (x.x%)
Two or more	x (x.x%)	x (x.x%)	x (x.x%)
Maximum toxicity grade, n			
Grade 1	x (x.x%)	x (x.x%)	x (x.x%)
Grade 2	x (x.x%)	x (x.x%)	x (x.x%)
Grade 3	x (x.x%)	x (x.x%)	x (x.x%)
Grade 4	x (x.x%)	x (x.x%)	x (x.x%)
Outcome, n			
Resolved	x (x.x%)	x (x.x%)	x (x.x%)
Not resolved	x (x.x%)	x (x.x%)	x (x.x%)
Fatal	x (x.x%)	x (x.x%)	x (x.x%)
Action taken with cytarabine, n			
Dose not changed	x (x.x%)	x (x.x%)	x (x.x%)
Temporarily interrupted	x (x.x%)	x (x.x%)	x (x.x%)
Permanently discontinued	x (x.x%)	x (x.x%)	x (x.x%)
Not applicable	x (x.x%)	x (x.x%)	x (x.x%)
Action taken with GRASPA®, n			
Dose not changed	x (x.x%)	x (x.x%)	x (x.x%)
Temporarily interrupted	x (x.x%)	x (x.x%)	x (x.x%)
Permanently discontinued	x (x.x%)	x (x.x%)	x (x.x%)
Not applicable	x (x.x%)	x (x.x%)	x (x.x%)

Diabetogenic effects will comprise diabetes mellitus, glucose and lipid increase. Pancreatic events will comprise clinical pancreatitis and asymptomatic (biochemical) pancreatitis.

5.8.2. Laboratory Data

5.8.2.1. Haematology, Coagulation, Biochemistry tests

Biological parameters will be described at inclusion, D1, D5, D9, D13, D18 and D23 of each course of chemotherapy. The concerned biological parameters are the followings:

- Haematology
  - Haemoglobin (g/dL)
  - Hematocrit (%)
  - Erythrocytes (T/L)
  - Leukocytes (G/L)
  - Neutrophils (G/L)
  - Blasts (%)
  - Platelets (G/L)
- Blood coagulation
  - Activated Partial Thromboplastin Time (aPTT) (sec)
  - Prothrombin time (%)
  - Fibrinogen (g/L)
  - Antithrombin III (%)
  - INR
- Blood biochemistry
  - Albumin (g/L)
  - Plasma Bicarbonate (mmol/L)
  - Creatinine clearance (mL/min)
  - Serum Creatinine
  - Glycaemia (mmol/L)
  - Alkaline Phosphatase (U/L)
  - AST (U/L)
  - ALT (U/L)
  - Cholesterol (mmol/L)
  - LDH (U/L)
  - Gamma-GT (U/L)
  - Bilirubin (µmol/L)
  - Triglycerides (g/L)
  - Sodium (mmol/L)
  - Potassium (mmol/L)
  - Calcium (mmol/L)
- Pancreas
  - Lipase (U/L)
  - Amylase (U/L)

Raw results as well as absolute and relative change from baseline will be described at each timepoint between treatment groups.

Absolute change in the biological parameter between visit V_i and baseline will be calculated according to the formula: *biological parameter at V_i – biological parameter at baseline*

Relative change in biological parameter between visit V_i and baseline will be calculated according to the formula: $\frac{\text{biological parameter at } V_i - \text{biological parameter at baseline}}{\text{biological parameter at baseline}} \times 100$

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values. Data will be summarized by treatment group and patients with laboratory values of NCI-CTCAE grade 3 or 4 will be identified.

5.8.2.2. Amino-acids and total blood asparaginase

This procedure is applicable to patients under GRASPA® treatment only.

Amino acids will be described at D11 and D18 of the first two cycles of chemotherapy on all patients, at D11 and D18 of every remaining cycle for patients included before the protocol amendment and at D13 and D27 of the first two cycles for patients included after the protocol amendment:

- asparagine
- aspartate
- glutamine
- glutamate

Total blood asparaginase will be described at D11 and D18 of the first two cycles of chemotherapy on all patients, at D11 and D18 of every remaining cycle for patients included before the protocol amendment and at D13 and D27 of the first two cycles for patients included after the protocol amendment:

- Plasmatic asparaginase
- Total asparaginase
- Encapsulated asparaginase
- Free asparaginase

Encapsulated asparaginase is defined as: *Total asparaginase - Plasmatic asparaginase*.

Free asparaginase is defined as: *Plasmatic asparaginase / Total asparaginase*

For lab values reported in the format BLLQ (Below Lower Limit of Quantification), the value of limitation should be used for the purpose of including this data in the calculation of summary statistics:

Parameters	Lower limit of quantification
Asparagine	0.519 µmol/L*
Aspartate	0.987 µmol/L*
Glutamine	49.802 µmol/L*
Glutamate	10.716 µmol/L*
Plasmatic asparaginase	2.5 U/L*
Total asparaginase	75 U/L *

* These data will depend of the central laboratory, and will be confirmed before analyses.

Raw results as well as absolute and relative change from D11 will be described at each time point between treatment groups, and presented separately for patients recruited before and after the protocol amendment.

Absolute change in biological parameter between D18 and D11 will be calculated according to the formula: *Biological parameter at D18 – Biological parameter at D11*

Relative change in biological parameter between D18 and D11 will be calculated according to the formula:

$$\frac{\textit{Biological parameter at D18 – Biological parameter at D11}}{\textit{Biological parameter at D11}} \times 100$$

5.8.3. Vital Signs and Physical Examinations

Raw results as well as absolute and relative change from baseline for weight, ECG, heart rate, systolic and diastolic blood pressure will be described at each visit between treatment groups.

Absolute change in vital signs between visit V_i and baseline will be calculated according to the formula: *Vital signs at V_i – Vital signs at baseline*

Relative change in vital signs between visit V_i and baseline will be calculated according to the formula:

$$\frac{\textit{Vital signs at } V_i \textit{ – Vital signs at baseline}}{\textit{Vital signs at baseline}} \times 100$$

By-subject listings of vital sign measurements will be presented in data listings and patients with vital sign values of NCI-CTCAE grade 3 or 4 will be identified.

5.8.3.1. Physical Examinations

Physical examination results at each time point will be summarized; shifts between baseline and a subsequent study visit in physical examination findings to will also be presented. All physical examination findings will be presented in a data listing.

5.8.4. Concomitant Medications

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.

Previous medications are defined as medications reported with a stop date prior or equal to the date of inclusion. In case of partial/missing stop date the following rules will be applied:

- If only the day is missing: month and year of stop date will be used to determine whether the medication is prior or concomitant
- If day and month are missing: the year of stop date will be used to determine whether the medication is prior or concomitant
- If the stop date is missing the medication will be considered as prior and concomitant

All other medications reported will be considered as concomitant. Previous and concomitant medications will be described in each treatment group according to their therapeutic class (ATC) and preferred term (PT) (WHO Drug Dictionary, version of March 2013).

The previous and concomitant medications will be summarized by treatment group in the ITT population.:

- The number and percentage of patients presenting at least one previous medication will be described in each treatment group.
    - The previous medication will then be presented per ATC and PT in a frequency table in each treatment group.
- The number and percentage of patients presenting at least one concomitant medication will be described in each treatment group.
    - The concomitant medication will then be presented per ATC and PT in a frequency table, in each treatment group.

The medications given for type II diabetes will be presented.

6. CHANGES TO PLANNED ANALYSES

Initially, this study was designed with Progression Free Survival as its primary endpoint. However, the protocol definition of PFS only considered death due to progression. It was recognised that this was not in line with regulatory guidance where death from any cause is included in the endpoint and the definition of PFS was therefore modified. Based on recommendations from the AML Advisory Board (meeting conducted on 24th January 2017) the primary endpoint was changed from PFS to overall survival.

A planned interim analysis for futility was not conducted.

7. REFERENCES

8. CLINICAL STUDY REPORT APPENDICES

8.1. Statistical Tables, Figures, and Listings to be Generated

Table/Figure Number	Output Title	Analysis Set
	Patient Information	
14.1.1.1	Overall Patients Disposition	All Patients
14.1.1.2	Patients Disposition by Investigator Centre	All Patients
	Protocol Deviations	
14.1.2.1	Summary of Deviations Related to Inclusion/Exclusion Criteria	ITT
14.1.2.2	Summary of Major Protocol Deviations – Reasons for Exclusion From Per Protocol Population	ITT
14.1.2.3	Listing of Patients Randomized but not Treated	ITT
	Demographic Data and Baseline Characteristics	
14.1.3.1	Patient Demographics and Baseline Characteristics	ITT
14.1.3.2	Disease Characteristics and AML Cancer History	ITT
	Prior Related Therapies	
	Medical History Related to Other Diseases	

Table/Figure Number	Output Title	Analysis Set
14.1.4.1	Summary of Medical History – Previous Condition	ITT
14.1.4.2	Summary of Medical History – Ongoing Condition	ITT
	Prior and Concomitant Medications	
14.1.5.1	Summary of Prior Medications	ITT
14.1.5.2	Summary of Concomitant Medications	ITT
	Treatment Compliance and Exposure	
14.1.6.1	Summary of Study Duration	Safety
	Treatment Exposure	
14.1.6.2.1	Summary of Exposure to GRASPA and Low Dose Cytarabine and Dose Intensity	Safety
14.1.6.2.2	Compliance, Dose Reductions and Interruptions of GRASPA and Low Dose Cytarabine	Safety
14.1.6.2.3	Listing of Patients with at Least One Dose Reduction or Interruption of GRASPA and Low Dose Cytarabine	Safety
	Efficacy Data	
14.2.1.1.1.1	Summary of Overall Survival by Treatment Group	ITT

Table/Figure Number	Output Title	Analysis Set
14.2.1.1.1.2	Summary of Overall Survival by Treatment Group	PP
14.2.1.1.2.1	Overall Survival by Treatment Group – Kaplan Meier Curves	ITT
14.2.1.1.2.2	Overall Survival by Treatment Group – Kaplan Meier Curves	PP
14.2.1.1.3.1	Summary of Overall Survival by Treatment Group – Cox PH Model with Prognostic Factors	ITT
14.2.1.1.3.2	Summary of Overall Survival by Treatment Group – Cox PH Model with Prognostic Factors	PP
14.2.1.1.4.1	Forest Plot of OS Hazard Ratios – Subgroup Analyses	ITT
14.2.1.1.4.2	Forest Plot of OS Hazard Ratios – Subgroup Analyses	PP
14.2.1.2.1.1	Summary of Disease Response and Duration of Response by Treatment Group	ITT
14.2.1.2.1.2	Summary of Disease Response and Duration of Response by Treatment Group – Subgroup Analyses	ITT
14.2.1.3.1.1	Summary of Progression Free Survival by Treatment Group	ITT
14.2.1.3.1.2	Summary of Progression Free Survival by Treatment Group	PP
14.2.1.3.2.1	Progression Free Survival by Treatment Group – Kaplan Meier Curves	ITT

Table/Figure Number	Output Title	Analysis Set
14.2.1.3.2.2	Progression Free Survival by Treatment Group – Kaplan Meier Curves	PP
14.2.1.3.3.1	Summary of Progression Free Survival by Treatment Group – Cox PH Model with Prognostic Factors	ITT
14.2.1.3.3.2	Summary of Progression Free Survival by Treatment Group – Cox PH Model with Prognostic Factors	PP
14.2.1.3.4.1	Forest Plot of Progression Free Survival Odds Ratios – Subgroup Analyses	ITT
14.2.1.3.4.2	Forest Plot of Progression Free Survival Odds Ratios – Subgroup Analyses	PP
14.2.1.4.1	Summary of Relapse Free Survival by Treatment Group	ITT
14.2.1.4.2	Relapse Free Survival by Treatment Group – Kaplan Meier Curves	ITT
14.2.1.5	Summary of Transfusion Needs by Treatment Group	ITT
14.2.1.6.1	Summary of Biomarkers	ITT
Figure 14.2.1.6.2	Biomarkers Over Time – Spaghetti Plots	ITT
	PK and PD Parameters	
14.2.9.1	PK and PD Parameters – Plasma and Blood – Summary Statistics Over Time	Safety

Table/Figure Number	Output Title	Analysis Set
14.2.9.2	PK and PD Parameters – Plasma and Blood – Patients with Asparagine Depletion	Safety
14.2.9.3	PK and PD Parameters – Immunogenicity	Safety
14.2.9.4	Summary of Biomarker Cytogenetic Testing	Safety
14.2.9.5	Summary of Bone Marrow Tumor Cell Parameters	Safety
	Quality of Life Questionnaires	
14.2.10	QLQ-C30 Absolute and Changes From Baseline	ITT
	Number of Hospitalizations	
14.2.11	Summary of Hospitalizations by Treatment Group	ITT
	Safety Data	
	Adverse Events	
14.3.1.1.1	Summary Analysis of Incidence of Treatment Emergent Adverse Events	Safety
14.3.1.1.2	Summary Analysis of Incidence of Treatment-Related Treatment Emergent Adverse Events	Safety
14.3.1.1.3	Summary Safety Analysis of GRASPA in combination with low-dose cytarabine	ITT

Table/Figure Number	Output Title	Analysis Set
14.3.1.2.1	Incidence of Treatment Emergent Adverse Events by Preferred Term	Safety
14.3.1.2.2	Incidence of Treatment Related Treatment Emergent Adverse Events by Preferred Term	Safety
14.3.1.2.3	Incidence of Treatment Emergent Adverse Events with Toxicity Grade of 3 or 4 by Preferred Term	Safety
14.3.1.2.4	Incidence of Treatment Related Treatment Emergent Adverse Events with Toxicity Grade of 3 or 4 by Preferred Term	Safety
14.3.1.2.5	Incidence of Treatment Emergent Serious Adverse Events by Preferred Term	Safety
14.3.1.2.6	Incidence of Treatment Related Treatment Emergent Serious Adverse Events by Preferred Term	Safety
14.3.1.2.7	Incidence of Treatment Emergent Adverse Events of Special Interest by Preferred Term	Safety
14.3.1.2.8	Incidence of Treatment Emergent Adverse Events of Special Interest with Toxicity Grade of 3 or 4 by Preferred Term	Safety
14.3.1.2.9	Incidence of Treatment Emergent Adverse Events Occurring in at least 5% of Patients in either Treatment Group by MedDRA Preferred Term	Safety
14.3.1.3	Listing of Treatment Emergent Adverse Events Leading to Either GRASPA or Chemotherapy Withdrawal	Safety

Table/Figure Number	Output Title	Analysis Set
	Deaths	
14.3.2.1	Deaths and Deaths within 28 Days After Last IMP Administration	Safety
14.3.2.2	Listing of All Deaths	Safety
	Clinical Laboratory Data	
	Biochemistry	
14.3.3.1.1	Biochemistry – Summary of Shift From Baseline to Worst Post-Baseline Results	
14.3.3.1.2	Biochemistry – Summary Statistics for Clinically Significant Parameters by Treatment Group and Time	
	Hematology	
14.3.3.2.1	Hematology – Summary of Shift From Baseline to Worst Post-Baseline Results	Safety
14.3.3.2.2	Hematology – Summary Statistics for Clinically Significant Parameters by Treatment Group and Time	Safety
	Coagulation	
14.3.3.3.1	Coagulation – Summary of Shift From Baseline to Worst Post-Baseline Results	Safety

Table/Figure Number	Output Title	Analysis Set
14.3.3.3.2	Coagulation – Summary Statistics for Clinically Significant Parameters by Treatment Group and Time	Safety
	Other Safety Parameters	
	Vital Signs Data	
14.3.4.1.1	Vital Signs – Descriptive Statistics for Change From Baseline	Safety
14.3.4.1.2	Vital Signs – Listing of Clinically Significant Values	Safety
14.3.4.2	ECOG Performance Status – Shift From Baseline to Worst Post-Baseline Value	Safety

8.2. Data Listings to be Generated

	Subject Data Listings	
	Subjects Disposition	
16.2.1.1	Patient Disposition and Analysis Sets	ITT
16.2.1.2	Subject Visit Dates	ITT

	Protocol Deviations	
16.2.2.1	Deviations Relating to Inclusion/Exclusion Criteria	All Patients
16.2.2.2	Other Protocol Deviations	ITT
	Demographic Data and Baseline Characteristics	
16.2.4.1	Demographic Data	ITT
16.2.4.2	Baseline Characteristics	ITT
16.2.4.3	Medical and Surgical History	ITT
16.2.4.3.1	Medical History Related to Primary Disease Condition	ITT
16.2.4.3.2	Medical History Related to Other Disease	ITT
16.2.4.3.3	Physical Examination	ITT
	Previous and Concomitant Medications	
16.2.4.4.1	Prior Medications	ITT
16.2.4.4.2	Concomitant Medications	ITT
	Compliance and/or Drug Concentration Data	
	Drug Exposure	
16.2.5.1.1	GRASPA Administration	Safety

16.2.5.1.2	Cytarabine Administration	Safety
	Efficacy Data	
16.2.6.1	Tumour Lesions Measurements	ITT
16.2.6.2	Tumour Assessment Responses – Investigator and Central Readings	ITT
16.2.6.3	PFS and Overall Survival – Time-to-Event Variables	ITT
16.2.6.4	PK and PD Parameters	Safety
16.2.6.5	Biomarker Parameters	Safety
16.2.6.6	Immunogenicity Parameters	Safety
16.2.6.7	Quality of Life – QLQ-C30	ITT
	Adverse Event Listings	
16.2.7.1	Treatment Emergent Adverse Events	Safety
	Clinical Laboratory Data	
16.2.8.1	Biochemistry Data (SI Units)	Safety
16.2.8.2	Hematology Data (SI Units)	Safety
16.2.8.3	Coagulation Data (SI Units)	Safety

	Other Safety Parameters	
16.2.9	Vital Signs Parameters and Weight Assessments	Safety