STUDY PROTOCOL PHASE IIb
GRASPA-AML 2012-01

A Multicenter, open, randomized, controlled phase IIb trial evaluating efficacy and tolerability of GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase) plus low-dose cytarabine vs low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) elderly patients, unfit for intensive chemotherapy
ENFORCE 1 study

N° EUDRACT: 2012-002026-78

Protocol Amendment no 4– date: 05 Oct 2015
Protocol Version 07, dated 05 Oct 2015

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2 NOV 2015
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List of Abbreviations

AE	Adverse Event
ALT	Alanine Amino-Transferase
ALL	Acute Lymphoblastic Leukemia
APL	Acute promyelocytic leukemia
AML	Acute myeloid Leukemia
AST	Aspartate Amino-Transferase
ASNS	Asparagine Synthethase
BM	Bone Marrow
CCG	Children Cancer Group
CBF-AML	Core binding factor acute myeloid leukemia
COG	Children Oncology Group
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Response
CRi	Complete Response with incomplete recovery
CRA	Clinical Research Associate
CRF / e-CRF	Case Report Form/electronic CRF
CTCAE	Common Terminology Criteria for Adverse Events
D / d	Day
DNA	Deoxyribonucleic acid
IDMC	Independent Data Monitoring Committee
EDC	Electronic Data Capture
EFS	Etablissement Francais du Sang (French Blood Bank)
EORTC	European Organization for Research and Treatment of Cancer
FAB	French American British (classification system for AML)
GCP	Good Clinical Practices
GGT (γGT)	Gamma-Glutamyl transpeptidase
HCT	Hematocrit
HIV	Human immunodeficiency virus
HiDAC	High dose cytarabine
HR	Hazard Ratio
IAST	Irregular Antibody Screening Test
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board – Independent Ethics Committee
ITT	Intend To Treat
IU	International Units
IWRS	Interactive web response System
kg	Kilogram
L-Asp	Asparaginase
L	Liter
LDAC	Low-dose Cytarabine
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndrome
mg	Milligram
mL	Milliliter
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PBBC	Peripheral Blood Blast Count
PCV	Per cell volume
PFS	Progression Free Survival

PK/PD(PK-PD)	Pharmacokinetics/pharmacodynamics
PP	Per Protocol
PR	Partial remission
PS	Performance status
PT	Prothrombin time
PT	Preferred Term
(a)PTT	(activated)Partial Thromboplastin Time
PVC	Polyvinyl Chloride
QoL	Quality of Life
RBC	red blood cells
RD	Resistant Disease
RFS	Relapse free survival
mRNA	Messenger Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit Normal
vs	versus
WHO	World Health Organization

1. Synopsis

Study Identifier	GRASPA-AML 2012-01
Study Title	A multicenter, open, randomized, controlled phase IIb trial evaluating efficacy and tolerability of GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase) plus low-dose cytarabine *vs* low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) elderly patients, unfit for intensive chemotherapy.
Investigational Product	GRASPA®, eryaspase (proposed INN)
Study Rationale	Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells and the most common malignant myeloid disorder in adults. The median age at presentation for patients with AML is about 65 years (Estey 2006). Standard therapy for older patients with AML has a poor outcome, and for those who cannot undergo intensive chemotherapy, any alternative to palliative treatment need to be investigated. For the last 30 years, L-asparaginase (L-Asp) has held a key role in chemotherapy for Acute Lymphoblastic Leukemia (ALL). Some leukemic cells, with asparagine synthetase deficiency, need plasma L-asparagine for protein synthesis. L-Asp hydrolyses L-asparagine leading to depletion of this amino acid. Normal cells are resistant to L-asparaginase because they can synthesize asparagine using asparagine synthetase. L-Asp is an integral component of induction treatment of ALL in children and young adults (< 55 years). Capizzi (1988) has reported a significant benefit of L-Asp in AML. One hundred ninety-five adult patients with refractory or first AML relapse were randomly assigned to receive high-dose cytarabine (HiDAC), 3 g/m^2 as a three-hour intravenous (IV) infusion every 12 hours for four doses, followed by 6,000 IU/m² L-Asp administered at hour 42, or HiDAC without L-Asp. Treatment was repeated on day 8. There was an overall superior complete remission (CR) rate for HiDAC/L-Asp (40%) vs HiDAC (24%), p = .02. Subset analysis according to prior response and age showed the following CR rates: 54% from HiDAC/L-Asp treatment of refractory AML in patients less than 60 years, and 31% in patients greater than 60 years; CR from HiDAC in the same refractory groups were 18% (less than 60) and 0% (greater than 60). There was an overall survival benefit for patients treated with HiDAC/L-Asp (19.6 weeks) compared with HiDAC (15.9 weeks), p = .046, primarily attributable to effects in refractory patients. Toxicity in the two treatment arms was comparable. Another study with HiDAC plus asparaginase in elderly patients with newly diagnosed acute non-lymphocytic leukemia has been performed by the Italian Cooperative Group GIMEMA (Petti 1989). Overall, 43/125 evaluable patients (34.4%) achieved CR. Single case reports have been published that demonstrate the potential benefit of L-asparaginase in different AML or mixed lineage leukemia (Horikoshi 2009, Rubnitz 2009) Antitumor activity of GRASPA as well as any L-asparaginase is based on depletion of plasma asparagine, which is an essential amino acid for cells survival in almost all lymphoblastic cells. This may also apply to other type of cancer cells including myeloid leukemia cells. A study with GRASPA in elderly ALL (GRASPALL-GRAAL SA2 2008) showed that efficacy/safety profile of 100 and 150 IU/Kg was positive, both doses achieving

	sustained plasma asparagine depletion over 7 days with no excessive limiting toxicities.
Study Design	Open label, Randomized 1:2, controlled Phase IIb clinical trial. 24-months follow-up
Study Objectives	**Primary**: To evaluate Overall Survival (OS) in AML patients 65 to 85 years old unfit for intensive chemotherapy, when treated with GRASPA plus low-dose cytarabine compared to low-dose cytarabine alone. **Secondary**: To evaluate: • Response to treatment • Progression-free Survival (PFS) • Relapse Free Survival • Patient transfusion needs • Patients Quality of life evolution • Number of hospitalization • 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)
Study population	123 patients randomized 1:2, i.e. 41 patients treated with low-dose cytarabine alone in Arm A and 82 patients treated with GRASPA plus low-dose cytarabine in Arm B
Main Inclusion Criteria	• Patient ≥ 65 years old and ≤ 85 years old • Newly diagnosed Acute Myeloid Leukemia (AML) or post myelodysplastic syndrome diagnosed within 6 months prior to study enrollment • Unfit for intensive chemotherapy (at risk to suffer treatment related pejorative toxicities /early death) due to the presence of one or more of the following criteria: o Dependence in activities of daily living owing to the presence of comorbidities other than those resulting from the deterioration caused by the neoplastic disease. o Presence in the patient's medical history of three or more of the following comorbidities, even if they are under control with proper treatment: ▪ Congestive heart failure ▪ Other chronic cardiovascular diseases ▪ Chronic obstructive pulmonary disease ▪ Cerebrovascular disease ▪ Peripheral neuropathy ▪ Chronic kidney failure ▪ Hypertension ▪ Diabetes mellitus ▪ Systemic vasculitis ▪ Severe arthritis

	○ Presence of geriatric syndromes such as fecal or urinary incontinence, spontaneous bone fractures, mild and moderate dementia, or patients who fall repeatedly. OR Patient unwilling to receive intensive chemotherapy • Eligible to receive low-dose cytarabine treatment • ECOG performance status ≤ 2 • Female patients of childbearing potential and males must agree to use adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for the duration of study treatment and for 6 months after the last dose of Cytarabine or 3 months after last dose of GRASPA (whichever is the longest). • Negative serum pregnancy test at study entry for female subjects of childbearing potential • Subscription to social security insurance (if applicable, in accordance with local regulations) • Ability to understand, and willingness to sign, a written informed consent document and to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
Main Exclusion Criteria	• Patients with M3 AML of FAB classification (APL, acute promyelocytic leukemia) • Patients with AML involving chromosome 16 abnormalities or translocation (8:21) (CBF-AML) • Patient with secondary AML subsequent to prior malignant blood disorder such as: ○ Myelodysplastic syndrome diagnosed more than 6 months before study entry ○ Myeloproliferative syndrome • Prior therapy to AML (standard therapy or investigational agents) • Inadequate organ function : ○ Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis. ○ Serum creatinine concentration > 2 x ULN (Upper Limit of Normal) ○ AST or ALT levels > 3.5xULN or 5xULN if related to AML ○ Total bilirubin > 2 x ULN ○ INR > 1.5, unless patient under chronic treatment with anticoagulants (in this case, INR should be within expected ranges for the specific condition) ○ Insulin-dependent or uncontrolled diabetes mellitus • Concurrent malignancies other than AML requiring chemotherapy • Severe active infection, HIV seropositivity, or known active type B or C viral hepatitis • Known or suspected hypersensitivity or intolerance to mannitol • Breastfeeding or lactating women
Location	EUROPE

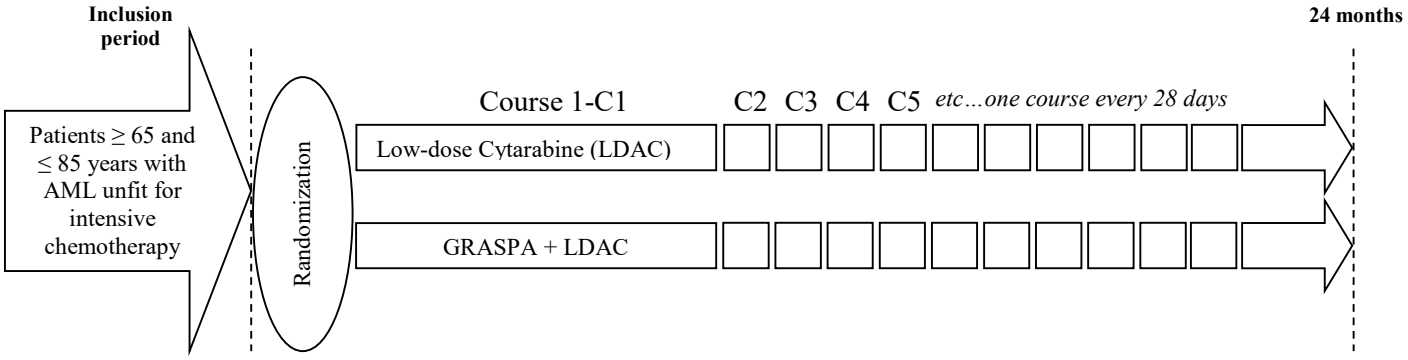
Study duration	Each patient will be followed for 24 months in the study.
Study Treatment	In the experimental group, the patients will receive one injection of GRASPA (100 IU/kg) in combination with subcutaneous low-dose cytarabine (same posology as reference group hereafter), every 28 days.
Control	In the control arm, patients will be treated with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months. Each period of 28 days constitute a cycle of chemotherapy. The dosage could be adjusted to 20 mg once daily in case of toxicities; higher dose is acceptable if required by patient's status, at investigator's decision.
Primary endpoint with time point assessment	**<u>Primary endpoint</u>**: • Overall survival (OS) defined as the time elapsed between randomization and death from any cause • The primary analysis for OS will take place once all patients have completed 12 months in the study **<u>Secondary endpoint</u> :** • Percentage of patients with Complete remission (CR), Complete remission with incomplete recovery (neutrophil or platelet regeneration, CRi), Partial remission (PR) • Progression-free survival (PFS) defined as the time elapsed between randomization and resistant disease or relapse or death from any cause • 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 • Percentage of patients who need transfusions (red cells and/or platelets), number of transfusion by patient • Patient quality of life (patient survey) • Number of hospitalizations (except scheduled protocol visit) • Safety of GRASPA® in combination with low-dose cytarabine, with specific attention to: o Grade 3 or 4 of Pancreatic toxicity o Grade 3 or 4 of hepatic toxicity, allergic or transfusion reaction or coagulation event o Grade 3 or 4 of hypoproteinemia or hyperglycemia/diabetes o All other non-hematologic Grade 4 toxicities (*NB* grading reference used : NCI CTCAE version 4.0) • Pharmacodynamic and pharmacokinetic parameters of GRASPA: o Plasma concentrations of asparagine, aspartate, glutamine, glutamate o Whole blood L-asparaginase activity • Immunogenicity : titer of anti-L-asparaginase antibodies • Asparagine synthetase, Asparagine synthetase mRNA expression and *in vitro* sensitivity to asparaginase on the harvested bone marrow cells (optional) • Biomarker cytogenetic testing (optional)
Treatment discontinuation	Patients will discontinue study treatment in the following situations: • Disease relapse or presence of a resistant disease, unless the investigator considers that the patient has a clinical benefit from continuing the treatment. In this case, the investigator should continue to perform the same

	study visits as long as considered clinical beneficial. • Occurrence of GRASPA-related toxicity, such as: o Grade 3 or 4 pancreatic toxicity o Grade 3 or 4 hepatic toxicity, allergic reaction, or coagulation event o other non-hematologic Grade 4 toxicity Patient assessment should continue as planned until evidence of relapse or presence of a resistant disease, in which case, patient will be followed up for survival. • Patient unwilling to continue • No evidence of study treatment benefit at investigator's decision
Statistical plan	**Sample Size** The sample size calculation has been based on the original primary efficacy endpoint (PFS) and a study that included an interim analysis for futility. We assumed 75% improvement in median PFS in the GRASPA plus low-dose cytarabine group compared to median PFS in the low-dose cytarabine group (control). With a two-sided 5% level significance test and a power of 80%, taking into account the unbalanced group size (2 : 1) and interim analysis a total of 123 patients should be enrolled (82 in the GRASPA plus low-dose cytarabine and 41 in the low-dose cytarabine group). **Analysis plan** The primary objective of the trial is to estimate whether GRASPA plus low-dose cytarabine is more promising than low-dose cytarabine alone with respect to OS in subjects 65-85 years old, with newly diagnosed AML unfit for intensive chemotherapy. The study however is not powered explicitly for OS and statistical significance in favor of GRASPA plus low-dose cytarabine is not anticipated. 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. Efficacy data from this study will be summarized and analyzed on an intention-to-treat (ITT) basis using randomized treatment while safety data for this study will be summarized using treatment received. The analysis of OS will be performed using a stratified log-rank test (stratification factor PS (performance status, 0, 1 vs 2). A secondary analysis will be performed using Cox's proportional hazards regression model, allowing for the effect of treatment and prognostic factors. For the main criterion of efficacy the significance level will be 0.05 using a two-sided test. OS will be summarized using Kaplan-Meier methods. PFS will be analyzed as a secondary criterion of efficacy. The primary analysis of the primary endpoint and the main secondary endpoints for efficacy will take place once all patients have completed 12 months in the study. A further supportive set of analyses will take place following completion of 24 months in the study for all patients. There will be no interim analysis for either futility or efficacy.
External Data monitoring board	An Independent Data Monitoring Committee (IDMC) will review the safety and tolerability of GRASPA at the following time points: - when 30 patients have been enrolled, to evaluate limiting toxicities as defined in stopping rules ,

	- when 60 patients have been enrolled. An original remit of the IDMC was to review the efficacy of GRASPA following 60 PFS events accrued. The IDMC meeting will still take place following the accrual of these events, but with remit of safety review only. Thereafter, the IDMC will convene every 6 months for safety review. Specific attention will be paid on patients with type II diabetes treated with oral hypoglycemic agents: IDMC will assess 5 first of those patients enrolled after at least one month follow-up, and may reconsider study enrollment of such patients. To avoid any conflict between the evaluation of safety and the primary efficacy endpoint OS, deaths in the study will be presented to the IDMC only in terms of overall frequencies and individual patient narratives. In particular Kaplan-Meier curves and p-value comparisons of those curves will not be presented. The IDMC will work completely independently of the sponsor. Sponsor representatives will not attend those meetings of the IDMC where study data aggregated by treatment group will be considered.
Date of Initiation	Q1 2013
Planned Date of completion	Q1 2018 (last patient last visit) Recruitment duration = 36 months + 24 months follow-up

2. Trial diagram

Figure 1: Study diagram



Patients included in the study will undergo successive courses of study treatment, for a duration up to 24 months. A course is defined as 28 days, with Day 1 being the first day the patient receive low-dose cytarabine (Figure 1: Study diagram).

Patient will have to attend a visit once a month, at the start of each course.

When study treatment is stopped (see required conditions in section 8.9), the visits will take place every 3 months until the 24 months study duration has been reached.

Refer also to section 8 for study treatment and assessments.

3. Introduction and rationale

3.1 Acute Myeloblastic Leukemia (AML)

Acute myeloid leukemia (AML) is a cancer involving hematopoietic progenitor cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, and its incidence increases with age. The median age at presentation for patients with AML is about 65 years.

The symptoms of AML are caused by replacement of normal bone marrow with leukemic cells, which causes decreased production of red blood cells, platelets, and normal white blood cells. The symptoms include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Several risk factors and chromosomal abnormalities have been identified, but the specific cause is not clear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated.

AML has several subtypes; treatment and prognosis varies among subtypes. Five-year survival varies from 15–70%, and relapse rate varies from 33–78%, depending on subtype.

In patients younger than 60 years, treatment consists in cytotoxic "chemotherapy" and might cure 20-75%, depending primarily on leukemia cell cytogenetic characteristics. Chemotherapy aimed at inducing a remission; patients may go on to receive additional chemotherapy or a hematopoietic stem cell transplant.

However, chemotherapy produce such a result in less than 10% of elderly patients because of their inability to survive treatment and, mainly, the association of old age with cytogenetic abnormalities involving chromosomes 5 and 7 (Estey, 2006).

Age over 60 years has constantly been identified as an independent adverse prognostic factor in AML, and there are very few long-term survivors in this age group. Poor outcomes in elderly AML patients have been attributed to both host- and disease-related factors, including medical comorbidities, physical frailty, and higher frequency of adverse cytogenetic characteristics. Most AML patients over 60 years die within a year and overall survival in this age group has not increased significantly during the last three decades (Roboz, 2011).

Older patients with multiple poor-risk factors have a poorer prognosis and treatment outcome. In a retrospective analysis of 998 old patients treated with intensive induction at the M. D. Anderson Cancer Center, multivariate analysis identified age over 75 years, unfavorable karyotype, poor performance status, creatinine > 1.3 mg/dL, duration of antecedent hematologic disorders > 6 months, and treatment outside a laminar airflow room as adverse prognostic factors. Patients with 3 or more of these factors had expected complete remission rate of less than 20%, 8-week mortality > 50% and one year survival < 10% (Kantarjian, 2006).

Efforts have been made to develop efficacious regimens that are tolerable for older patients. The prototype for low-intensity induction over the last several decades has been low-dose cytarabine, which resulted in complete remission rate of 18% and improved overall survival when randomized to supportive care and hydroxyurea (Burnett, 2007).

3.2 L-asparaginase in AML treatment

L-asparaginase activity is based on its catalytic activity for degrading asparagine and glutamine in blood and tissue liquids into aspartic and glutamic acid and ammonia, which thus induce a cytotoxic response against asparagine-dependent tumors. Survival and growth of most of leukemic cells, such as lymphoblasts as well as certain solid cancer cell lines, are asparagine-dependent, using this amino acid as nutriment for protein synthesis. This degradation is mainly evidenced by their asparagine depletion levels. This asparagine depletion results in a regression of leukemic cell proliferation (Broome, 1981) by several mechanisms involved in the destruction of tumor cells following treatment: inhibition of protein biosynthesis and subsequently, induction of apoptosis (Story, 1993).

Conversely, normal cells are resistant to L-asparaginase as they can synthesize asparagine using asparagine synthetase (ASNS) from other amino acids (glutamine or aspartic acid) when the level of serum asparagine is lowered. However some cancer cells are lacking ASNS and therefore when they are deprived of L-asparagine for growth and DNA replication, they become apoptotic and die.

A potential interest in AML has been identified from therapeutic use of free L-asparaginase and some bibliographic data. It has been demonstrated that AML blasts, especially M5 subtype cells, display a low level of ASNS (Codegoni 1995; Dubbers 2000; Kaspers 1999 Zwaan 2000). Kitoh *et al.* (1996) performed immunocytochemical staining in AML samples and showed that FAB M1, M4 and M5 cells were negative for ASNS. This supports the results of Okada *et al.* (2003) showing the relative sensitivity of M1, M4 and M5 cells to L-asparaginase and strongly suggests that ASNS expression is inversely correlated with sensitivity to L-asparaginase in AML cells.

Several cooperative groups have studied the combination of L-asparaginase with other induction chemotherapy regimen used in first-line and relapse AML, both in adults and in children. In adults, Capizzi (1988) has reported a significant benefit of L-asparaginase in AML. One hundred ninety-five adult patients with refractory or first AML relapse were randomly assigned to receive high-dose cytarabine (HiDAC), 3 g/m² as a three-hour intravenous (IV) infusion every 12 hours for four doses, followed by L-asparaginase 6,000 IU/m² (L-Asp) administered at hour 42, or HiDAC without L-Asp. Treatment was repeated on day 8. There was an overall superior complete remission (CR) rate for HiDAC/L-Asp (40%) vs HiDAC (24%), P = .02. Subset analysis according to prior response and age showed the following CR rates: 54% from HiDAC/L-Asp treatment of refractory AML in patients less than 60 years, and 31% in patients greater than 60 years; CR from HiDAC in the same refractory groups were 18% (less than 60) and 0% (greater than 60). There was an overall survival benefit for patients treated with HiDAC/L-Asp (19.6 weeks) compared with HiDAC (15.9 weeks), P = .046, primarily attributable to effects in refractory patients. Toxicity in the two treatment arms was comparable.

Another pilot study with high-dose cytarabine plus asparaginase in elderly patients with acute non-lymphocytic leukemia newly diagnosed has been performed by the Italian Cooperative Group GIMEMA (Petti *et al.*, 1989). Overall 43/125 evaluable patients (34.4%) achieved CR. In addition a synergistic efficacy of L-asparaginase with cytarabine when used sequentially has been observed in this study.

The Children Oncology Group (COG) published a review (Wells *et al.*, 1993) to determine the impact of high-dose cytarabine and L-asparaginase intensification on the outcome of childhood AML. Three consecutive Children Cancer Group (CCG) trials in AML: CCG 251 (1979 to 1983), CCG 213P (1983 to 1985), and CCG 213 (1985 to 1989) with a total of 1,294 patients enrolled, were reviewed. Inclusion of the 7-day interval cytarabine/L-asparaginase intensification was accompanied by an overall improvement in 5-year survival rates from diagnosis when compared with historical controls (CCG 213, 36% vs CCG 251, 29%, P < .02).

In children, L-Asparaginase is currently used in AML treatment protocols (protocol ELAM 02 2010).

Others single case reports have been published recently, pointing out the potential benefit of L-asparaginase in different AML or mixed lineage leukemia (Horikoshi *et al.*, 2009, Rubnitz *et al.*, 2009, Takahashi *et al.*, 2012).

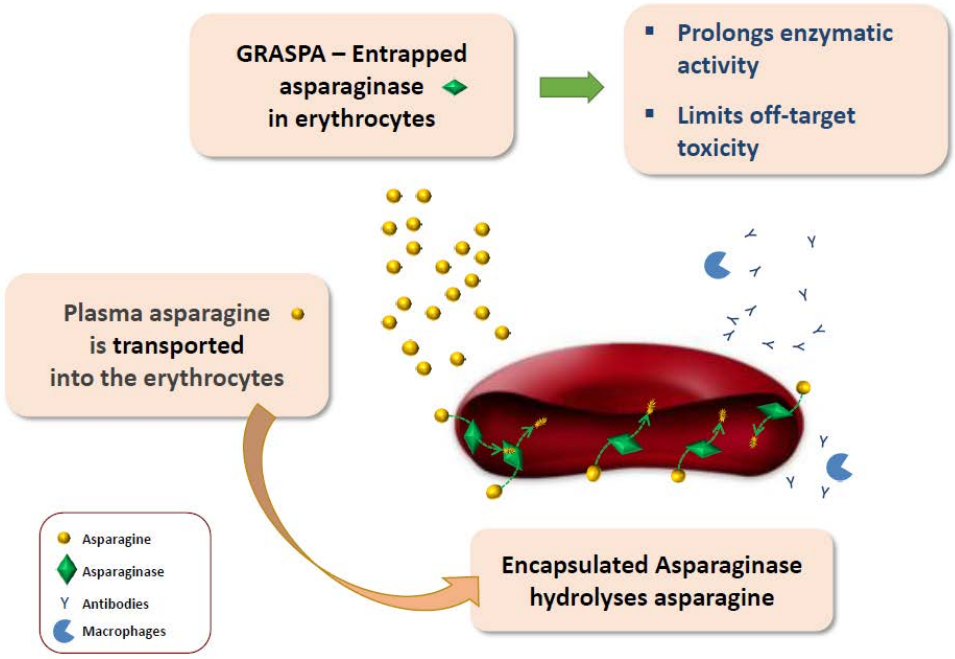
3.3 GRASPA, a new formulation of L-asparaginase

GRASPA is a ‘circulating microbioreactor’. As shown in Figure 2, plasma asparagine is actively pumped through the membrane of the erythrocyte into the intracellular compartment where it is cleaved by entrapped L-asparaginase. The erythrocyte membrane protects L-asparaginase against fast degradation/elimination, hence allowing for a long circulating activity and a longer half-life than with free L-asparaginase. Thus, GRASPA combines the capacity of erythrocytes to actively ‘pump’ asparagine from blood plasma through sodium-coupled neutral amino acid transporters and the enzymatic activity of entrapped L-asparaginase to cleave asparagine into aspartic acid and ammonium leading to plasma asparagine depletion. This encapsulation concept is not considered as a ‘slow release’ of the L-asparaginase, since the activity of asparagine degradation takes place within the erythrocyte, until the latter is removed in the same manner as normally transfused erythrocytes, by macrophages or dendritic cells in the liver or spleen. The encapsulation of L-asparaginase eliminates the direct somatic contact with the L-asparaginase, and it is hypothesized that this provides the potential to reduce toxicity associated with the parent L-asparaginase and prolong the activity of the enzyme (Figure 2).

Several tumor types depend on circulating asparagine for their growth and survival. In particular, leukemic cells are deficient in asparagine synthetase enzyme and are therefore incapable of synthesizing asparagine

(Stams *et al*. 2005, Kumar *et al*. 2014). The L-asparaginase treatment is based on the conversion of circulating asparagine into aspartic acid and ammonia, which deprives cancer cells of their source of asparagine and leads to their growth arrest and apoptosis. Normal cells are protected from asparagine requirement due to their ability to produce this amino acid with the help of the ASNS (Kawedia and Rytting 2014).

Figure 2: Mechanism of action of GRASPA



One main advantage of encapsulating L-asparaginase into erythrocytes is to reduce hypersensitivity reaction to asparaginase, as the L-asparaginase is protected from the immune system by the erythrocyte membrane. Additionally, its active site is preserved, potentially resulting in lower production of neutralizing antibodies and reduction in the frequency and severity of hypersensitivity reactions. Although the enzyme retains its intrinsic immunogenic potential, it is no longer expressed as the erythrocyte membrane prevents its recognition by the immune surveillance systems of the host.

3.4 GRASPA Current Clinical Experience

Four clinical trials have been conducted with GRASPA in Europe, in pediatric, adult and elderly patients with ALL – Table 1.

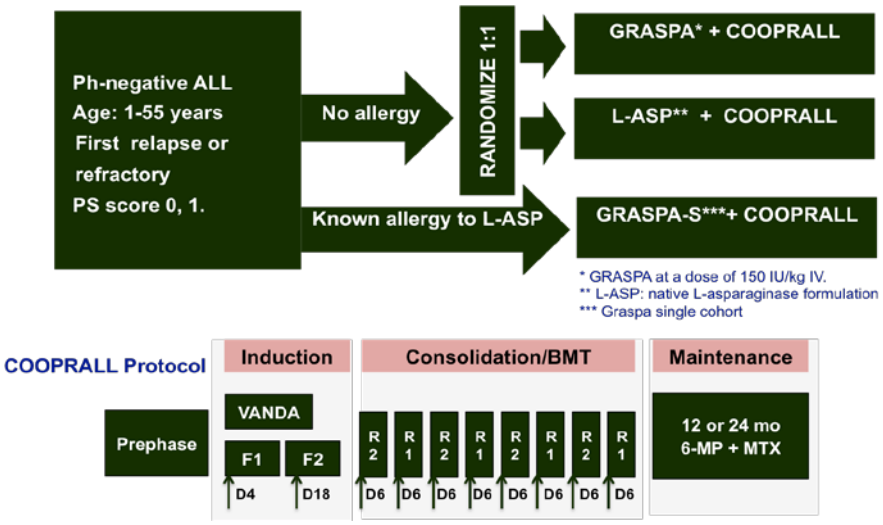
Table 1: Clinical trials with GRASPA in ALL indication

Study reference	Type of study /population	Status
GRASPALL 2005-01	GRASPALL 2005-01: Administration of allogenic red blood cell-loaded L-asparaginase in patients with relapsed acute lymphoblastic leukemia (ALL) A Phase I/II multicenter, randomized study in adults and children over 1 year of age. N= 24 patients (GRASPA:9 children and 9 adults; native apsaraginase:3 children and 3 adults)	Completed
GRASPALL GRAALL SA2 2008	An escalating dose Phase IIa study of GRASPA added to multi-agent chemotherapy during induction phase for the	Completed

	treatment of elderly patients, aged 55 years and over, presenting with Philadelphia chromosome-negative ALL. N= 30 patients	
GRASPALL 2009-06	A multicenter, open, randomized, Phase IIb/III study, evaluating efficacy and safety of GRASPA versus native L-asparaginase treatment in combination with multi-agent chemotherapy in patients with first recurrence of Philadelphia chromosome negative ALL N=80 patients (54 children and 26 adults). The randomized arms, n= 54 (GRASPA = 26; native asparaginase = 28)	Completed
GRASPALL2012-10-EAP Expanded Access Program	A multicenter, open, non-randomized study, evaluating safety of GRASPA in combination with multi-agent chemotherapy in patients under 55 years old with ALL at risk to receive other formulation of asparaginase.	Ongoing (13 patients enrolled)

The pivotal Phase III trial (**GRASPALL 2009-06)** is a randomized controlled trial, Figure 3.

Figure 3: GRASPALL2009-06 Study diagram



The co-primary endpoints were:

1. Duration (in days) of L-asparaginase activity >100 IU/L; and
2. Occurrence of study drug-related allergic reactions during the induction phase.

Key secondary endpoints included: MRD, complete remission rate, anti-asparaginase antibodies, adverse events, Events Free Survival and OS.

This trial enrolled 80 patients aged from 1 to 55 years, with either first relapse of Ph- ALL, or refractory to first-line treatment, and who were previously treated with native *E.Coli* L-asparaginase.

The mean duration of asparaginase > 100 IU/L measured in whole blood was significantly higher in GRASPA arm compared to control arm, with a mean (± SD) of 20.5 (5.2) days and 9.4 (7.4) days, respectively, p = 0.001. None of the patients (0/26) in the GRASPA arm had hypersensitivity reactions related to study drug during induction, compared to 13 (46.4%) in the control arm, p = 0.001. Patients in GRASPA arm achieved a higher CR (65.4%, 95% CI: [51.6:89.8]) as compared to control arm (39.3%, 95% CI: [23.3:63.1]), p=0.026.

The key adverse events of interest, generally considered to be a class-effect relevant to L-asparaginase, mainly included hypersensitivity reactions, coagulopathic events, pancreatic and hepatic events. The majority of these events occurred at a lower frequency with GRASPA compared to L-ASP, Table 2.

Table 2: Summary of key adverse events of interest that are study-related AEs in ≥ 10% of patients arranged by MedDRA Preferred Term

Preferred Term [a]	GRASPA N=26 (%)	Control native asparaginase N= 28 (%)
At least one AE	**19 (73.1)**	**28 (100)**
Hypofibrinogenemia	7 (26.9)	18 (64.3)
Elevated amylase and/or lipase enzyme elevation)	7 (26.9)	15 (53.6)
Transaminase increased	5 (19.2)	6 (21.4)
Hypoalbuminemia	4 (15.4)	9 (32.1)
Anti-thrombin III decreased	3 (11.5)	20 (71.4)
Hyperbilirubinemia	2 (7.7)	5 (17.9)
Drug hypersensitivity reactions	2 (7.7)	16 (57.1)
Hepatotoxicity	1 (3.8)	5 (17.9)
GGT increased	1 (3.8)	4 (14.3)
Activated partial thromboplastin time prolonged	1 (3.8)	3 (10.7)

Extras of Table 14.3.1.10.1 GRASPALL 2009-06 CSR

4. Objectives

4.1 Primary objective

To evaluate Overall Survival (OS) in AML patients 65-85 years old and unfit for intensive chemotherapy, when treated with GRASPA plus low-dose cytarabine compared to low-dose cytarabine alone.

4.2 Secondary objectives

- Response to treatment
- Progression-free survival
- 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)

4.3 Study endpoints

4.3.1 Primary endpoint

Overall survival (OS) is 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.

4.3.2 Secondary endpoints

- Percentage of patients with Complete remission (CR), Complete remission with incomplete recovery (neutrophil or platelet regeneration, CRi), Partial remission (PR)
- Progression-free survival (PFS) defined as the time elapsed between randomization and resistant disease or relapse or death from any cause
- 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
- Percentage of patients who need transfusions (red blood cells and/or platelets), number of transfusions by patient
- Patient quality of life evaluated using the EORTC QLQ-C30 version 3 scale
- Number of hospitalizations (except scheduled protocol visit) required during the study
- Safety of GRASPA in combination with low-dose cytarabine, with specific attention to :
    - Grade 3 or 4 of Pancreatic toxicity
    - Grade 3 or 4 of hepatic toxicity, allergic reaction or coagulation event
    - Grade 3 or 4 of hypoproteinemia or hyperglycemia/diabetes
    - All other non-hematologic Grade 4 toxicities

(*NB* grading reference used: NCI CTCAE version 4.0)

- Pharmacokinetic and pharmacodynamic parameters:
    - Plasma concentrations of asparagine, aspartate, glutamine, glutamate
    - Whole Blood L-asparaginase activity
- Immunogenicity by measuring titer of anti-L-asparaginase antibodies
- Biomarker cytogenetic testing (optional)
- Measurement of the following parameters on harvested bone marrow tumor cells (optional):
    - Asparagine synthetase protein expression
    - Asparagine synthetase mRNA expression
    - In vitro sensitivity to L-asparaginase

(See also section 8.8 for details)

Table 3 hereafter provides the definitions of response criteria in AML.

Table 3: Response criteria in AML

Category	Definition
Complete remission (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); red blood cell transfusion independence
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])
Partial remission (PR)	all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%
Resistant disease (RD)	BM blasts increase of at least 5% vs nadir AND/OR PBBC increase of at least 15% in absolute count vs nadir OR at least 50% in percentage vs nadir – repeated at min 7 days interval
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease
Stable disease	Failure to achieve at least Partial Remission AND no Resistant Disease criteria

* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.
¶ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML. (adapted Döhner *et al* 2010, Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet, Blood, 21 Jan 2010, vol 15, no 3; 453 – 474)

5. Benefit – risk analysis

5.1 Potential benefit for elderly patients with first AML diagnosis

In elderly AML patients with standard cytogenetic risk, treatment with intensive chemotherapy results in median overall survival of up to 12 months, whereas in the adverse cytogenetic category median survival is only 2-3 months (Lagadinou, 2010). The median age at presentation for patients with AML is about 65 years and in this age group, AML is associated with a poor prognosis. Therefore, AML in the elderly represents a major unmet medical need.

Asparaginase has been used in some treatment protocols for AML in children. Capizzi (1988) has reported a significant benefit of Asparaginase in AML. However, its use remains hampered due to its toxicity. The use of L-asparaginase has a potential interest in AML, in light of the fact that AML blasts display a low level of ASNS (see section 3.2).

GRASPA has been proposed as a new approach to maintain the activity of L-asparaginase while improving its safety profile. Recent experience of GRASPA in ALL with an elderly population >55 years, demonstrated a

tolerable safety profile. This study showed that GRASPA favorable safety profile of both doses 100 and 150 IU/Kg (GRASPALL 2007-04). A recent PK/PD re-analysis of all completed studies with GRASPA demonstrated that age has no impact on the PK of different dosing levels; and therefore, a dosing schedule of 150 IU/Kg every 2 weeks is proposed as a standard dose for all age groups.

The objective of the development of GRASPA in AML is evaluate the overall survival benefit and the both progression free survival and event free survival and patient quality of life, as well as assess the impact on ASNS profile of myeloblasts as an exploratory objective.

5.2 Potential risks for the patients

The Potential toxicity of GRASPA results from 2 main mechanisms: (1) toxicity related to L-asparaginase, (2) toxicity associated with erythrocyte.

5.2.1 Risk associated with L-asparaginase

When L-asparaginase (free formulation as *E. Coli* L-asparaginase) is given, major effects observed include mainly hypersensitivity reactions related to the direct immunogenicity of the compound and pancreatic, hepatic or coagulation disturbances, probably related, in part, to asparagine depletion (Kurtzberg 2007).

These toxicities are treatment-limiting especially in frail populations such as elderly patients.

The encapsulation of L-asparaginase (GRASPA) eliminates the direct somatic contact with the L-asparaginase, and it is hypothesized that this provides the potential to reduce toxicity associated with the parent L-asparaginase and prolong the activity of the enzyme. On the basis of the pharmacological effects of L-asparaginase, GRASPA is expected to have a therapeutic benefit in AML.

In study GRASPALL 2009-06, the incidence of allergic reactions was significantly lower in both GRASPA arms in the non-allergic (7.7%) and allergic patients (11.5%), as opposed to a rate of 57.1% in patients treated with native-asparaginase. There were no withdrawals due to hypersensitivity reactions, either in the allergic or non-allergic patient subsets. The most common drug-related events with GRASPA were hypofibrinogenemia (26.9%), asymptomatic pancreatitis (26.9%), elevated transaminases (19.2%), hypoalbuminemia (15.4%), and decreased anti-thrombin III (11.5%). By contrast, most of these events took place at greater incidence (64.3%, 53.6%, 21.4%, 32.1%, and 71.4% for hypofibrinogenemia, asymptomatic pancreatitis, elevated transaminases, hypoalbuminemia, and decreased anti-thrombin III, respectively). These results indicate that GRASPA is anticipated to have a favorable safety profile in patients with AML unfit to receive intensive chemotherapy.

5.2.2 Risk associated with erythrocytes administration

Blood transfusion can cause adverse effects, either related to the patient's particular condition, or to blood product, blood donor and blood transfusion procedure. These adverse events are well known (American Association of Blood Banks 1996; AFSSAPS 2003).

The quantity of encapsulating erythrocytes administered as GRASPA are reduced compared to those used in usual blood transfusion practices. The volume of erythrocytes (leukocyte-depleted RBC in a SAG-mannitol suspension) injected per unit of RBC (280 ml) corresponds to approximately 4.6 ml/kg of an 18 g/dL suspension (HCT/PCV 60%). Comparatively, an administration of GRASPA at a dose of 100 IU/kg and 150 IU/kg corresponds to 1.8 mL/kg, respectively 2.7 mL/kg of a 13 g/dL hemoglobin suspension (HCT/PCV 50%).

Safety data from 189 patients treated with GRASPA as of March 2015, all transfusion reactions occurred in 5.8% of the patients, of which 1.1% were serious. None of the AE was related to GRASPA.

Further, clinical studies with GRASPA have a clear guidance regarding monitoring of the patients during transfusions. In the event of transfusion reactions, transfusion must be stopped immediately and the necessary symptomatic treatments administered according to standard of care.

5.3 Benefit / Risk ratio

As of March 2015, a total of 189 patients have been treated with GRASPA in various indications. GRASPA has been developed to reduce L-asparaginase toxicities and, based on accumulated data so far, was shown to have an improved tolerability profile as compared to native L-asparaginase, with an important reduction in allergic reaction as well as reduction of coagulation disorders. As provided earlier, the safety and tolerability of GRASPA has been demonstrated in a Phase III trial in patients with ALL aged between 1-55 years, as well as in a Phase II study in elderly patients with ALL, aged over 55 years.

Therefore, based on the accumulated experience, the potential benefit of GRASPA outweighs the potential risks for assessing its clinical activity and tolerability in elderly patients with AML.

6. Trial design

6.1 Type of trial

This is a multicenter, open label, randomized, controlled phase IIb trial.

6.2 Experimental plan

The primary objective of the trial is to estimate whether GRASPA plus low-dose cytarabine is more promising than low-dose cytarabine alone with respect to OS in subjects 65-85 years old, with newly diagnosed AML unfit for intensive chemotherapy. The study however is not powered explicitly for OS and statistical significance in favor of GRASPA plus low-dose cytarabine is not anticipated. 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.

Efficacy data from this study will be summarized and analyzed on an intention-to-treat (ITT) basis using randomized treatment while safety data for this study will be summarized using treatment received.

The analysis of OS will be performed using a stratified log-rank test (stratification factor PS (0, 1 vs 2)) will be used to compare the two treatment arms.

A secondary analysis will be performed using Cox's proportional hazards regression model, allowing for the effect of treatment and possible prognostic factors. For the main criterion of efficacy the significance level will be 0.05 using a two-sided test. OS will be summarized using Kaplan-Meier methods.

PFS will be analyzed as a secondary criterion of efficacy using the same methods as for OS.

The primary analysis of the primary endpoint and the main secondary endpoints for efficacy will take place once all patients have completed 12 months in the study. A further supportive set of analyses will take place following completion of 24 months in the study for all patients.

There will be no interim analysis for either futility or efficacy.

7. Trial population

This trial will enroll patients corresponding to inclusion criteria AND exclusion criteria hereafter.

7.1 Inclusion criteria

To be eligible, patient must meet all the following criteria:

- Patient ≥ 65 years old and ≤ 85 years old.
- Newly diagnosed AML or post myelodysplastic syndrome (MDS) diagnosed within 6 months prior to study enrollment
- Unfit for intensive chemotherapy (at risk to suffer treatment related pejorative toxicities /early death), due to the presence of one or more of the following criteria:
    - Dependence in activities of daily living owing to the presence of comorbidities other than those resulting from the deterioration caused by the neoplastic disease.
    - Presence in the patient's medical history of three or more of the following comorbidities, even if they are under control with proper treatment:
        - Congestive heart failure
        - Other chronic cardiovascular diseases
        - Chronic obstructive pulmonary disease
        - Cerebrovascular disease

- Peripheral neuropathy
- Chronic kidney failure
- Hypertension
- Diabetes mellitus
- Systemic vasculitis
- Severe arthritis

- Presence of geriatric syndromes such as fecal or urinary incontinence, spontaneous bone fractures, mild and moderate dementia, or patients who fall repeatedly.

OR

Patient unwilling to receive intensive chemotherapy

- Eligible to receive low-dose cytarabine treatment
- ECOG performance status ≤ 2.
- Female patients of childbearing potential and males must agree to use adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for the duration of study treatment and for 6 months after the last dose of cytarabine or 3 months after the last dose of GRASPA (whichever is the longest)
- Negative serum pregnancy test at study entry for female subjects of childbearing potential
- Subscription to social security insurance (if applicable, in accordance with local regulations)
- Ability to understand, and willingness to sign, a written informed consent document and to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

7.2 Exclusion criteria

- Patients with M3 AML of FAB classification (APL, Acute Promyelocytic Leukemia))
- Patients with AML involving chromosome 16 abnormalities or translocation (8:21) (CBF-AML)
- Patient with Secondary AML subsequent to prior malignant blood disorder such as:
  - Myelodysplastic syndrome diagnosed more than 6 months before study entry
  - Myeloproliferative syndrome
- Prior therapy to AML (standard therapy or investigational agents)
- Inadequate organ functions:
  - Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis.
  - Serum creatinine concentration > 2x ULN (Upper Limit of Normal laboratory ranges),
  - AST or ALT levels > 3.5x ULN or > 5x ULN ,if related to AML
  - Total bilirubin levels > 2x ULN
  - INR > 1.5, unless patient under chronic treatment with anticoagulants (in this case, INR should be within expected ranges for the specific condition)
  - Insulin-dependent or uncontrolled diabetes mellitus
- Concurrent malignancies other than AML requiring chemotherapy

- Severe active infection, HIV seropositivity, or known active type B or C viral hepatitis
- Known or suspected hypersensitivity or intolerance to mannitol
- Breastfeeding or lactating women

7.3 Assignment to patient numbers

For confidentiality purpose, complete name of patient enrolled will not be revealed and patient data will be identified with a dedicated patient number in trial records.

Patient number will be composed of 6 digits: first 4 digits corresponding to site number, last 2 digits corresponding to the first number available following that of previous patient included in the trial in the same site. The number will be generated through Interactive Web Response System (IWRS), when minimal data patient are entered.

In countries where this practice is authorized by local regulations, patients may also be identified with initials.

7.4 Assignment to treatment schedule (randomization)

The patients will be randomly and sequentially allocated to either one of the two treatments A or B.

Randomization 1:2 will be performed by an Interactive Web Response System (IWRS, refer to Appendix 2 for randomization process).

After confirmation of randomization, the system will display the treatment arm assigned namely A or B as follows:

A: Low dose cytarabine (see section 10.1)

B: Low dose cytarabine + GRASPA

As poor performance status had been identified as a risk factor that increase probability of early death, and to avoid unbalance between groups, a stratified randomization will be done according to performance status (PS = 0 or 1 *vs* PS = 2).

7.5 Sample size

The study will enroll approximately 123 patients, see section 15.2 for sample size calculation.

7.6 Patient replacement

The target recruitment is 123 patients. Randomization will continue until 123 patients are recruited and they receive at least one course of treatment

8. Trial assessments

8.1 Visit flow chart and assessment

Table 4: Calendar of study 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 5: Calendar of study PK/PD assessments

Course after amendment implementation – protocol version 07				
Course 1 and 2				
	D11	D13	D18	D27
before admin	15 min +/- 10 min			
after end of Graspa admin:	5 min +/- 2 min	48 h +/- 2h	7 Days +/- 2h	16 days after first admin +/- 2h
	1 h +/- 10 min			
	3 h +/- 10 min			
	6 h +/- 10 min			

Table 6: 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 Table 4 and Table 5.

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. Assessments required are provided in Table 6.)

8.2 Inclusion period

The inclusion will take place before treatment beginning in order to obtain patient consent for study participation, verify the inclusion/exclusion criteria and gather the baseline data.

8.3 Registration procedure in IWRS (interactive web response system)

Registration takes place once the patient give his/her consent to participate in the study. Investigator must declare patient inclusion by entering patient data selection in IWRS (see details in Appendix 2) and, after checking all inclusion/exclusion criteria, ask for randomization.

After confirmation of randomization, the system will display the treatment arm allocated and the investigator will receive an e-mail.

A: Low-dose cytarabine

B: Low- dose cytarabine + GRASPA

8.4 Study treatment administration

All patients enrolled, randomized in Arm A or B, will receive successive 28-day courses of subcutaneous low-dose cytarabine 40 mg daily (or 20 mg twice daily) for 10 days per course (from day 1-D1 to day 10-D10), each course occurring every 28 days +/- 3 days, for a duration up to 24 months. SPC for Cytarabine Hospira and Pfizer are attached in Appendix 1 as example. Please refer to country-specific approved Cytarabine SPC for country-specific information.

Following the implementation of Amendment 4, patients randomized in arm B treatment will receive subcutaneous low-dose cytarabine, as described above, and GRASPA 100 IU/kg, given as an intravenous infusion at **Day 11** of each 28-day course.

Required documents such as **Investigator's prescription of GRASPA and Patient's pretransfusional status** (refer to section 9.6) should be sent at ERYTECH Pharma 2 days before the schedule day of GRASPA administration, i.e. Day 9.

In the event the patient cannot receive GRASPA treatment at the planned date (i.e. manufacturing failure) or if GRASPA treatment received on site is not suitable for administration (e.g. transport or cold chain impairment, rupture of bag…), investigator and ERYTECH Pharma will discuss the best treatment approach for the patient:

- Restart manufacture for a new bag of GRASPA (delay GRASPA administration with max one week), if acceptable for the patient.
- Switch the patient to appropriate alternative treatment, at investigator's decision.
    - If the switch occurred before the first GRASPA administration, then the patient will be replaced, as defined in section 7.6.
    - If the switch occurred after at least one administration of GRASPA, treatment for next blocks afterwards will be at investigator's decision (GRASPA will not be resumed if delayed more than 2 weeks; refer to section 8.5.4 "Dosage modifications of GRASPA" and 8.11 "end of study treatment").

8.5 Dosage modification in case of toxicity

8.5.1 General dispositions

- The investigator will carefully monitor treatment toxicity according to standard practice and to the schedule to assessment (section 8.1).
- Supportive therapy and adjustment to concomitant therapies may be prescribed by the investigator according to standard practice.

8.5.2 Transfusion reactions

The clinical symptoms of a transfusion reaction are variable. A few clinical signs of adverse reaction due to transfusion are listed here:

- Feeling of heat, malaise, feeling of burning along the vein
- Chills, fever with or without lumbar and thoracic pain
- Abrupt change in blood pressure, hypertension or hypotension
- Respiratory distress with dyspnea
- Urticarial, rash, localized or extensive edema
- Nausea with or without vomiting
- Hemorrhagic syndrome with bleeding at the site of injection and surgical wound.
- Anaphylactic shock

In case of any transfusion reaction, the first measure to be taken during the administration of GRASPA is to stop the transfusion immediately and then to administer the necessary symptomatic treatments, according to standard of care.

8.5.3 Dosage modifications for cytarabine

- Cytarabine dosage modifications should be applied according to the prescribing information and standard practice. At investigator judgment, if required by patient status, cytarabine dosage increase is acceptable.
- A standard recommendation, in case of toxicity attributed to cytarabine, is to reduce the dosage of cytarabine to 20 mg daily.
- In case of persistent or excessive toxicity attributed to cytarabine, cytarabine may be temporarily or permanently discontinued, as per investigator judgment. In such case, for patients in arm B, GRASPA should be continued as scheduled, every 14 days.

8.5.4 Dosage modifications for GRASPA

- If patient cannot receive GRASPA, for another reason than an adverse event, treatment may be postponed no later than one week after the initial scheduled day. A minimum two weeks interval between GRASPA infusions must be insured.
- In case of allergic reaction during administration, stop the administration immediately and then to administer the necessary symptomatic treatments, according to standard of care. Further administration of GRASPA will be at investigator judgment, considering possibility of premedication anticipated for such case.
- In case of any Grade 3 or 4 adverse event related to GRASPA occurring in two successive infusions, GRASPA should be discontinued.
- In the event of bilirubin levels >3 times upper limit of normal or transaminase levels >10 times upper limit of normal, treatment with GRASPA should be discontinued.

8.6 AML assessment

Initial bone marrow aspirate/biopsy must be available within four weeks prior randomization, for baseline blast count.

AML assessment will be performed for each course, in order to allow AML disease evaluation and response to treatment based on adapted Dohner criteria (see Table 3 for Response criteria definitions)

8.7 Laboratory assessments

8.7.1 Biological parameters

Biological assessment will be performed according to the investigational center procedure at inclusion, and then, at D1, D5, D9, D13, D18, D23 and D27 of each course of chemotherapy (± 2 days).

Following measurement should be performed:

- Hematology: Complete Blood Count (CBC), platelets;
- Coagulation parameters: Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), fibrinogen, antithrombin III, INR;
- Chemistry: bicarbonate, sodium, potassium, calcium, creatinine, creatinine clearance (calculated by Cockroft & Gault formula) , albumin, bilirubin, alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), lactate dehydrogenase, glucose, cholesterol, triglyceride, lipase, amylase;
- Serologic test for HIV, B and C hepatitis will be made at inclusion only, if needed.
- Serum pregnancy test for women with childbearing potential – at inclusion and end of treatment.

Assessed and signed anonymized lab reports must be sent to sponsor/representatives as soon as possible after receiving the results for protocol required tests as well as for any testing performed for management of AEs.

8.7.2 Pharmacokinetic, pharmacodynamic and Immunogenicity parameters

These procedures are applicable only to patients randomized on GRASPA treatment arm and they consist in the following tests:

- Amino acids levels: asparagine, aspartate, glutamine, and glutamate
- Whole blood asparaginase
- Anti-L-asparaginase antibodies

The Appendix 3: Samples preparation for centralized analyses summarizes parameters, procedures and central laboratories involved (a lab manual also is also edited and provided to investigational center).

NOTE: on the scheduled days for GRASPA administration, samples should be taken at least 5 minutes prior administration.

8.8 Patients Quality of Life

Patients will complete quality of life (QoL) questionnaire (EORTC QLQ-C30, version 3, Appendix 4) at each visit.

Also the number of transfusions (packed RBC or platelet) received by the patient will be recorded along the study as well as hospitalization (except scheduled for protocol visit).

8.9 Biomarker assessments

Bone marrow biopsy/aspirate will be collected at study entry and will be analyzed for biomarker analysis of potentially relevant biomarkers, utilizing proteomic, and transcriptomic techniques. Assays designed to evaluate biomarkers that may correlate with clinical outcome will be performed, including:

- Asparagine synthetase (ASNS) expression by two different methods: real-time qRT-PCR for the quantification of ASNS mRNA and western-blot for the quantification of ASNS protein expression (performed at The University of Texas MD Anderson Cancer Centre and Erytech Pharma respectively).
- Mutational analyses and detection of gene amplification of relevant oncogenes, e.g *FLT3, NPM1, IDH or KIT*

- Depending on tissue availability, additional assays may be performed, including immunohistochemistry (IHC), gene expression profiling, and transcriptomic profiling.
- Other potential biomarkers, as new scientific data emerge.

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.

Assessments could be repeated on further bone marrow aspirate if possible.

Please refer to Appendix 3 (Samples preparation for centralized analyses) as well as to lab manual for details regarding procedure of samples collection, handling, storage, shipping and central laboratory involved.

8.10 Study visits assessments and procedures

- Inclusion Visit (within max 4 weeks before treatment initiation):

  During the inclusion visit, the following procedures/assessments will be performed:

  - Patient information about potential study participation and obtaining the signed informed consent before any study related procedures;
  - Patient demographics: date of birth, gender;
  - ECOG performance status
  - AML characteristics and assessment (see section 8.6): qualitative and quantitative parameters, primary diagnostic date, baseline values for bone marrow blast count, cytogenetic analysis, FAB and WHO classifications, including extramedullary AML assessment
  - Medical history (relevant for the study condition) and concomitant medications
  - General physical examination by systems and organs, including routine ECG, weight and height measurements
  - Biological assessment (see section 8.7.1 for detailed items): date of sample taken; assessed and signed anonymized lab reports must be sent to sponsor/representatives - Inclusion and exclusion criteria validation
  - Patient registration in IWRS system
  - Patient randomization - if all criteria are met.

- Subsequent visits : from visit 1 onwards:

  - Disease evaluation (AML) (see section 8.6)
  - Clinical assessment: vital signs (height, weight, pulse, blood pressure systolic and diastolic), performance status (ECOG score), physical examination findings
  - Study treatment administration (low-dose cytarabine +/- GRASPA): details on date and time of administration are required
  - Patient quality of life: survey EORTC QLQ-C30, transfusion needs, hospitalizations from any cause (except scheduled protocol visit)
  - Biological assessment at D1, D5, D9, D13, D18, D23, D27 (see section 8.7.1 and table 4 for detailed items) – instructions to be provided to patient in case of lab testing outside the site hospital; assessed and signed anonymized lab reports must be sent to sponsor/representatives as soon as possible after sampling
  - PK-PD and immunogenicity testing (see section 8.7.2, Table 4 and 5 and Appendix 3 for detailed instructions) – only patients on arm B (under GRASPA treatment)
  - IAST (Irregular Antibodies Screening Test) at D9 - only patients on arm B (under GRASPA treatment)
  - Review and assessment of any adverse event (refer to section 11 for details)
  - Record of any change in concomitant medications
  - Distribution of patient diary and instructions provided to patients for completion – for each visit
  - Collection and Review of previous patient diary completed

- End of study treatment

  - Disease evaluation (AML) (see section 8.6)
  - Clinical assessment: vital signs, performance status (ECOG score), physical examination findings

- Patient quality of life: survey EORTC QLQ-C30, transfusion needs, hospitalizations from any cause (except scheduled protocol visit)
- Primary reason for treatment termination
- Subsequent AML treatment if any
- Collection and Review of previous patient diary completed
- Review and assessment of any adverse event (refer to section 11 for details)

- Follow-up visit after end of study treatment (every 3 months +/- 2 weeks after End of Treatment visit – ex. M3, M6, M12…)
  - Disease evaluation, in the case relapse/recurrent status had not already occurred and the patient was discontinued from the treatment for other reason
  - Patient quality of life: survey, transfusion needs, hospitalizations from any cause (except scheduled protocol visit)
  - Clinical assessment: Survival status
  - Review and assessment of any adverse event (refer to section 11 for details)
  - At minimum, a phone call will be performed 4 months (+/- 1 week) after end of treatment, for safety assessments

8.11 End of study treatment

Patients will stop study treatment in following situations:

- Disease relapse or presence of a resistant disease, unless the investigator considers that the patient has a clinical benefit from continuing the treatment. In this case, the investigator should continue to perform the same study visits as long as considered clinical beneficial.
- Occurrence of GRASPA-related toxicity, such as:
    - Grade 3 or 4 pancreatic toxicity
    - Grade 3 or 4 hepatic toxicity, allergic reaction, or coagulation event
    - other non-hematologic Grade 4 toxicity

    Patient assessment should continue as planned until evidence of relapse or presence of a resistant disease, in which case, patient will be followed up for survival.
- Patient unwilling to continue
- No evidence of study treatment benefit at investigator's decision

9. Investigational product: GRASPA

9.1 Pharmaceutical form, qualitative and quantitative composition

GRASPA is a dispersion for infusion of eryaspase, packed in transparent PVC bag designed for blood product, containing a single dose for one administration.

Each bag of GRASPA contains:

- Active substance: eryaspase, at a dose equivalent to 100 IU/kg of L-Asparaginase.
- Preservative solution: SAG Mannitol

The Red Blood Cell (RBC) source material is from leukocyte-depleted packed red blood cells, prepared and qualified by a blood bank. Selected RBC source material is compatible with the patient (blood type and results of irregular antibodies screening test).

The final volume of GRASPA bag depends on patient weight.

9.2 Posology

GRASPA is a ready to use suspension designed to be fully injected.

The dose of GRASPA is 100 IU/kg. In this study protocol, patients will receive one infusion of GRASPA on Day 11 of 28-day course of chemotherapy (see section 10.1).

9.3 Packaging and labeling

GRASPA is packaged in PVC (polyvinyl chloride) bags designed for blood product. Three removable segment-tubes are available and attached for checking before administration.

Label statements are specific to the clinical trial, complying with legal requirements for medicinal product. In addition they display specific items necessary for traceability of source cell material and medicinal product (blood group, patient's initials and birthdate). These mentions allow for checking the identity before administration.

9.4 Contra Indications

GRASPA should not be used in the following situation:

- History of Grade 4 hypersensitivty reaction to L-asparaginase
- Pregnancy/breastfeeding (see section 11.4)

9.5 Precaution for use

Anaphylaxis or serious allergic reactions: Patients should be constantly monitored during the infusion and at least one hour after the end of the infusion. Discontinue GRASPA with serious allergic reactions.

Coagulation disorders: Blood count and clotting profile should be monitored before and during treatment with GRASPA. In cases of anti-thrombin III deficiency, administration of anti-thrombin III concentrate is preferable to transfusion of fresh frozen plasma (FFP) as it could counteract the GRASPA activity.

Hepatotoxicity: Hepatic enzymes should be monitored before and regularly during treatment with GRASPA. Treatment with GRASPA should be discontinued in the event of bilirubin levels >3 times upper limit of normal or transaminase levels >10 times upper limit of normal.

Pancreatitis: Serum lipase and amylase should be monitored regularly. Treatment with GRASPA should be discontinued in patients with Grade 4 pancreatitis.

Glucose intolerance: L-asparaginase may cause hyperglycemia and patients with diabetes may have aggravation of their condition. Blood glucose levels should be monitored regularly.

Cardiac or renal impairment: Patients should be monitored for evidence of volume overload. The speed of infusion of GRASPA should be slowed as needed.

If a patient receives a blood transfusion between the prescription of GRASPA and its administration, new compatibility tests must be performed.

9.6 Prescription

GRASPA is manufactured for one patient at a time according to investigator's prescription.

To initiate the manufacture, ERYTECH Pharma should be provided with the documents listed hereafter:

- **Prescription Sheet** indicating patient identifiers as well as his weight, the investigator recipient of the product, the place and the time of delivery. A template of the prescription sheet is available in Appendix 5: Prescription of GRASPA
- Validated Erythrocyte phenotype and **ABO blood group card** with 2 determinations
- an **IAST (Irregular Antibody Screening Test)** performed at the local immunohematology laboratory, less than 72h prior to GRASPA transfusion

In the event the IAST is positive, or in case of previous or history of positivity, a compatibility test is mandatory. Therefore, a 5 mL sample of patient's blood should be sent to EFS Lyon (Service Immuno-hématologie, Hôpital Edouard Herriot pavillon I, place d'Arsonval – 69003 LYON. N° Fax: +33 (0)4 72 11 75 36 n° Tel: +33 (0)4 72 11 75 31)

9.7 Supply, transportation, receipt and storage conditions

GRASPA bag is shipped to Investigator's site in a qualified box allowing keeping medicinal product at controlled temperature +2°C to +8°C. The temperature evolution during shipment is continuously monitored by a recording sensor inside the pack.

Details regarding GRASPA reception should be documented by the recipient on the document "GRASPA Shipment and administration Form" (Appendix 6):

- Patient information consistency
- The integrity of the bag of GRASPA (absence of visual leak),
- The temperature indicator attached to the bag must show no sign that the product underwent out of range temperature. Otherwise, the investigator must contact ERYTECH Pharma for further instructions.
- The expiry date is compatible with the date and time of administration
- Presence of control card and Infusion double line (allowing the rinsing)

Presence of a Packaging for bag return

GRASPA should be managed and administered by the physician-investigator's department as soon as possible upon receipt and within the expiry time stated on the label.

The current shelf life of the product is 72 h from end of manufacture when stored between +2 °C to +8 °C (See the mention on the label).

GRASPA can be kept at room temperature up to a maximum of 6 hours before the injection (including the injection time). The product remains stable as showed in the stability studies. Do not freeze.

Instruction for receipt and administration of GRASPA are detailed in Appendix 6. Any issue happen, please contact ERYTECH Pharma for immediate appropriate recommendation.

9.8 Administration

Before administration of GRASPA, the following controls must be performed and should be recorded on the document "GRASPA Shipment and administration Form" (Appendix 6):

- The general appearance of the bag. The statements on the label are adapted according to the clinical trial.
- The product for color; dark red color should be observed. If it provides evidence that the product underwent excessive or low temperatures during shipment, the investigator must contact ERYTECH Pharma for further instructions. He/she will then determine whether to urgently request a new preparation.
- Presence of the document "GRASPA Shipment and Administration Form".

  Consistency of information on "GRASPA Shipment and Administration Form" and the patient: name, forename, date of birth.
- An ultimate cross match blood test to check compatibility. Expiry date is compatible with date and time of administration.

  If there is any doubt, the product must not be administered.

A compatibility test (cross-match) test between the patient's blood and GRASPA (removable segment tubes) should be performed in your local laboratory and GRASPA must not be administered in case of discrepancy.

GRASPA should not be administered beyond the maximum shelf life stated on the label.

GRASPA should not be transferred to another container before injection. Since no data regarding incompatibility are available, GRASPA should not be mixed or administered simultaneously with any other product, solution or medicinal product.

The administration should take place within the expiry time stated on the label of GRASPA.

GRASPA is administered by intravenous route using line devices provided with the product, under medical responsibility. If a pump is used, only devices specifically approved for blood transfusion should be used.

The rate of transfusion depends on the patient's clinical conditions. The mean duration for administration is about 45 minutes, longer in case cardiac impairment and must be adapted regarding the volume of the bag and patient's clinical conditions.

The entire content of the bag must be administered. The patient must remain awake and should be constantly monitored during the injection for occurrence of any adverse reactions and should be kept under observation for at least one hour post administration. In case of occurrence of a major symptom (e.g. malaise), GRASPA injection should be stopped immediately and the principal investigator must be informed.

At the end of the injection, the lines should be rinsed with 20-40 ml of physiological saline solution (0.9% NaCl).

The responsible person in charge of administration should record on "GRASPA Shipment and administration Form" (Appendix 6) information below:

- date and the time of injection
- name of the responsible person in charge of latest verifications before injection
- Whether the entire content was injected and the lines accurately rinsed, with full explanation if it was not the case.

Then this document should be faxed immediately to ERYTECH Pharma to confirm GRASPA administration.

N° Fax: +33 (0)4 78 78 93 05

9.9 Traceability documentation on site

Traceability of reception controls and administration of GRASPA is documented with the document "Shipment and administration Form" (Appendix 6).

This document should be archived in the patient medical file.

This document could be duplicated as needed and forwarded to the responsible persons concerned.

The investigator is responsible for GRASPA accountability at the trial site.

9.10 Return of empty package and accountability

Empty bags must be returned to ERYTECH Pharma after GRASPA injection, using the material supplied to this attention. The bags will be checked for accountability and weighing at ERYTECH Pharma.

9.11 Case of non-administration of GRASPA

In case a bag of GRASPA is not administered to the patient, this event will be documented accordingly, providing full explanations for such case. Such case will be reported to EFS Lyon Rhône Alpes as well. These unused bags of GRASPA will be destroyed on site (biohazardous waste) or sent back to ERYTECH Pharma the same way as empty bags.

In case of any issue, resulting in the quality of the product being compromised, the product must not be administered. Investigator should contact ERYTECH Pharma who will organize product return. Investigator will assess the delay in case of a new production need to be sent, and if it is not acceptable he will decide the best treatment for her/his patient.

9.12 End of study treatment

Refer to section 8.11 for details

10. Concomitant medication

10.1 Cytarabine chemotherapy

All patients enrolled are to be treated with low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) subcutaneously for 10 days per course, each course occurring every 28 days (+/- 3 days).

The dosage could be adjusted to 20 mg once daily in case of toxicities at investigator's decision. Also, increased dose is acceptable if required by patient’s status, as per investigator judgement.

10.2 Concomitant treatments during study

Concomitant medications requiring precautions:

- Oral Anticoagulants: fluctuations of coagulation factors and risk of thrombosis should be monitored with repeated measurements of INR
- Erythropoiesis stimulating agents except if deemed necessary by the investigator
- Growth Cell Stimulating Factors, except in case of severe infection at investigator's decision

Prohibited concomitant medications:

- Other antineoplastic agents
- Other L-asparaginase marketed products
- Other investigational product

10.3 Interactions

10.3.1 Contraindication:

A single GRASPA administration may lead to anti-L-asparaginase antibody production. These can trigger allergic reactions (mild reaction to anaphylactic shock) when another injection of L-asparaginase (whatever the form) administration is given. It is fully contra indicated to administrate any form of E. Coli L-asparaginase without a prior antibody test.

Yellow fever Vaccination: risk of fatal systemic vaccine disease.

10.3.2 To be avoided:

Vaccination with live vaccines: increase risk of serious infection especially in immunodeficient patients. Inactivated vaccines are preferred when available.

11. Safety

11.1 Adverse Events (AE)

11.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Any worsening, in frequency or severity, pre-existing condition should also be considered as an adverse event when occurring in patient administered a medicinal product.

Adverse Drug Reaction: Any noxious and unintended response to a medicinal product related to any dose administered. The phrase response to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

11.1.2 Collection, recording and reporting of AE

11.1.2.1 Collection of Adverse Events

The following AE will be taken into account for this trial (grading reference used is the NCI-CTCAE version 4.0):

Any event will be recorded, irrespectively of the relationship with GRASPA / low dose cytarabine according investigator's opinion AND the grade. Similarly, any reaction linked to red blood cells (see section 11.3) during GRASPA administration will be recorded as an AE in the CRF.

Laboratory tests abnormalities

Any abnormal laboratory value should be reported as an AE.

- EXCEPTION: When ALL the following criteria, the investigator may decide not to be reported such the abnormal value:
  - The abnormal parameter IS part of the schedule of assessment AND
  - Is NOT associated with clinical symptoms AND
  - Is considered NOT medically significant by the Investigator, AND
  - Does NOT result in change of GRASPA / Low-dose cytarabine or other concomitant treatment administration

Disease Progression

In this study, the signs and symptoms corresponding to the disease progression or worsening (AML) **should not be recorded as AEs**. Death related to disease progression should not be reported as SAE.

The following **should not be recorded as AEs**, if recorded at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Pre-existing stable conditions found as a result of screening procedures. Worsening of preexisting conditions must be reported.

If seriousness criterion is met, a SAE should be declared to ERYTECH Pharma drug safety, completing SAE report form (see section 11.2 and Appendix 7).

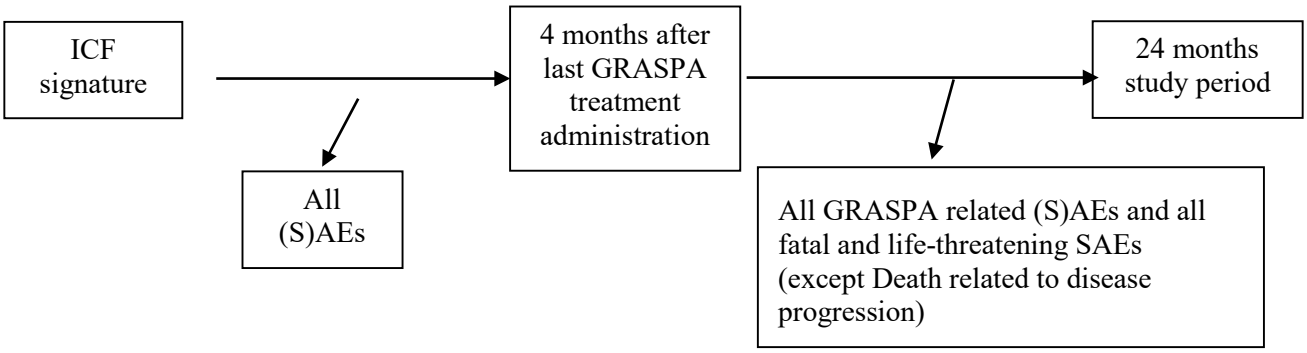
11.1.2.2 Recording procedure

Any event meeting the definition of an AE / SAE must be collected and reported from subject signature of the informed consent and until 4 months after last GRASPA/ low-dose cytarabine administration (see Figure 4).

Any AE / SAE **related to GRASPA** according to investigator's opinion must be collected and reported throughout study duration.

Any SAE leading to death or life threatening must be collected and reported throughout study duration.

Figure 4: Safety reporting timeline guide



All AE / SAE must be followed until resolution or the end of the protocol. The Investigator should ensure that adequate medical care is provided to the subject for any adverse event.

If there are several events and different symptoms combined to a main AE, then the only main AE (diagnostic preferable if available) should be recorded in the CRF. Where there is no link between different clinical symptoms occurring at the same time, each sign should be recorded as separate AE.

Occurrence and follow-up of AE should be assessed at each visit, and essential data listed hereafter should be recorded in the patient's CRF and patient's medical file as well:

- the severity or grade of the adverse event,
- the causality: determination of whether an adverse event is related to the investigational treatment or procedure, or other agents are suspected of causing the adverse event,
- the action(s) taken regarding investigational product (continued / interrupted / stopped)
- the corrective treatment if any
- the event outcome
- the seriousness of the event

11.1.2.3 Intensity /AE grading

Grade is used to denote the severity of the adverse event. The NCI Common Terminology Criteria for Adverse Event (NCI CTCAE) v. 4.0 will be used as reference for AE grading in this trial. If the term does NOT appear in the NCI CTCAE, the AE is graded using the following categories:

- **1 / Mild**: minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic only; marginal clinical relevance
- **2 / Moderate**: minimal intervention; local intervention; noninvasive intervention (packing, cautery),
- **3 / Severe**: significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation). The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria (see section 11.2).

- **4 / Life-threatening or disabling**: complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or surgery.
- **5 / Fatal**

11.1.2.4 Causality assessment

Causality is the determination of whether an adverse event is related to a medical treatment or procedure. Causality categories are:

- **Reasonable possibility:** where the AE is clearly (certainly), likely to be (probably) or could be (possibly) related to the treatment or procedure.
- **No reasonable possibility:** where the AE is clearly NOT (not related) or doubtfully (unlikely) related to the treatment or procedure.
- In the case it is impossible to judge the AE causality, due to lack of information, or inconsistent information which cannot be investigated further, the AE/SAE will be reported as **possibly related**.

11.1.2.5 Outcome

The event outcome is mandatory and should be recorded as soon as it gets resolved, where appropriate when the subject has completed the protocol at the latest. The outcome should be one of the following:

- **Recovering**: the AE is improving
- **Not yet recovered**: the AE is still ongoing when the subject has completed the protocol.
- **Recovered**: fully recovered or by medical or surgical treatment the condition has returned to baseline level.
- **Recovered with sequelae**: as a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be declared as an SAE (see section 11.2).
- **Fatal**: any AE resulting in death should be declared as an SAE (see section 11.2).

11.2 Serious Adverse Events (SAE)

11.2.1 Seriousness criteria

An adverse event is classified as "serious" when at least one the following criterion is met:

- **Results in death**: be aware that a death cannot be an event but always the outcome of an event. Exception is when death occurs suddenly, without the exact cause is stated. In this case only, the event should be recorded as "sudden death" with the seriousness criterion "fatal" indicated.
- **Is life-threatening**: life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization.**
- **Results in persistent or significant disability/incapacity.**
- **Is a congenital anomaly or birth defect.**
- **Is considered as serious according investigator judgment in other situation**. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above, should also be considered serious.

11.2.2 SAE procedures (notification)

In addition to be recorded in patient's CRF, as well as any Adverse Event, Serious Adverse Event will be recorded in a separate SAE form (Appendix 10), and declared to ERYTECH Pharma, whether attributed to the protocol or not.

Therefore, an SAE report must be completed and faxed without delay and in any case within 24 hours of obtaining knowledge about the event to:

SAE FAX No: +33 (0)4 67 10 72 53 or email to erytech@vigipharm.fr

(Vigipharm mandated by ERYTECH Pharma)

If necessary, Investigator will be asked for additional information. SAE Follow-up report will be then completed and faxed to ERYTECH Pharma in the same way as the initial report.

Any documentation regarding SAE, initial and follow-up report, should be archived together with patient's source documents.

ERYTECH Pharma is responsible for declaring all Unexpected Serious Adverse Reactions (treatment related events) to Competent Authorities (and Ethical Committee(s) as needed), in accordance with the local requirements. Investigators will be informed as well.

11.2.3 SAE follow-up

Investigator should ensure that adequate medical care is provided to the subject for any adverse event.

All SAE must be followed until the subject has recovered, stabilized, recovered with sequelae or died. The Investigator must forward follow-up information on SAE to ERYTECH Pharma without delay and in any case within 24 hours of obtaining the new information. SAE Follow-up report should be faxed accordingly to:

SAE FAX No: +33 (0)4 67 10 72 53 or email to erytech@vigipharm.fr

(Vigipharm mandated by ERYTECH Pharma)

11.3 Event linked to red blood cells during GRASPA administration

Any adverse event that may be related to erythrocytes / blood transfusion should be assessed by the investigator according to the clinical background of the patient. In such cases, the Appendix 8 summarizes the corresponding procedure:

- Any event linked to red blood cells will be recorded in the CRF as an AE. If seriousness criterion is met, a SAE should be declared to ERYTECH Pharma drug safety, completing SAE report form (see section 11.2.2 above).
- The return of the bag of GRASPA to ERYTECH Pharma will be organized for immunologic and hematologic analyses.
- If additional analyses are required in local laboratory, segment tubes can be removed from the bag of GRASPA for this purpose.

11.4 Pregnancy - Lactation

Since no preclinical or clinical data are available, GRASPA IS NOT TO BE USED during pregnancy and lactation.

Cytarabine has known teratogen effects in several animal species and IS NOT TO BE USED during pregnancy and lactation

11.5 Trial premature withdrawal

The trial can be prematurely stopped (definitely or temporarily) when:

- The treatment is considered as too noxious to continue with further clinical investigations

- Occurrence of new fact that can modify ERYTECH Pharma / Competent Authority approval on the trial, or for any unethical reason
- ERYTECH Pharma decision to stop product development

In case of any reason motivating such withdrawal, the Investigator should promptly inform the patients, ensure appropriate therapy and follow-up, and complete the CRF with all available data at the time of trial arrest.

Trial withdrawal with the reason will be declared to Competent Authority (and EC if applicable) in accordance with local requirements.

11.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will review the safety and tolerability of GRASPA at the following time points:

- when 30 patients have been enrolled, to evaluate limiting toxicities as defined in stopping rules ,
- when 60 patients have been enrolled.

The original remit of the IDMC was to review the efficacy of GRASPA following 60 PFS events. The IDMC meeting will still take place following the accrual of these events, but with remit of safety review only. Thereafter, the IDMC will convene every 6 months for safety review

Specific attention will be paid on patients with type II diabetes treated with oral hypoglycemic agents: IDMC will assess 5 first of those patients enrolled after at least one month follow-up, and may reconsider study enrollment of such patients.

To avoid any conflict between the evaluation of safety and the primary efficacy endpoint OS, deaths in the study will be presented to the IDMC only in terms of overall frequencies and individual patient narratives. In particular Kaplan-Meier curves and p-value comparisons of those curves will not be presented.

The IDMC will work completely independently of the sponsor. Sponsor representatives will not attend those meetings of the IDMC where study data aggregated by treatment group will be considered. A specific document will be edited separately providing IDMC members details and conditions for such evaluation during IDMC meetings.

11.7 Development Update Safety Report (DSUR)

ERYTECH Pharma will forward to Competent Authority and Ethic Committee Development Update Safety Report on GRASPA with all available safety information, in accordance with local requirements.

ERYTECH Pharma will keep investigators informed about data available impacting subject's safety.

Occurrence of any new fact about research conduct or investigational product use, likely to cause subject's safety impairment will be taken into account to initiate appropriate action to guarantee subject's safety. ERYTECH Pharma will immediately inform Competent Authority and Ethic Committee as well as investigators.

12. Case Record Form (CRF)

CRF will be used to collect data. Any assessment and corresponding results performed during protocol visits as stated in the schedule (detailed in section 8) will be recorded in patient medical file (source document) in order to be integrated in the Case Record Form.

All laboratory data and Investigator observations must be reported to sponsor. Any imaging techniques must be summarized in the CRF where applicable. The original reports, traces and films must be retained by the Investigators for future reference.

Some data may not be included in source document but could be recorded in the CRF directly. Such data need to be defined before study start. The CRF will be then considered as a part of source document.

This trial will use an e-CRF, i.e. based on electronic data capture (EDC), designed and provided by ERYTECH Pharma or contractors. All requested data should be entered in the CRF on a regular basis, as soon as they are obtained, by the investigator or an authorized delegated person. The Investigator or authorized staff must ensure that all information recorded is consistent with the source information.

At the end of the study, each CRF will be edited for archiving purposes, in accordance with local requirements.

13. Monitoring procedures

During the course of the trial, a dedicated CRA will visit investigational sites to monitor study conduct as it progresses. The purpose of these visits is to ensure:

- Subjects enrolled were duly informed and gave their consent,
- Adherence to protocol and GCP guidelines are followed,
- CRF completion is accurate (consistency of data recorded *versus* source document),
- SAE are notified accordingly if any,
- Drug accountability is well documented, and documentation regarding investigational product is present and complete,
- Any problems detected in the course of the monitoring visits are resolved.

Therefore, the Monitor must be given direct access to source documents (original documents, data and records, see section 16). Direct access includes permission to examine, analyze, verify and reproduce any record(s) and report(s) that are important for clinical trial evaluation.

Investigator must be available for discussions and clarifications over the phone as well.

The following data can be recorded directly on the CRF and will be considered as source data: Vital signs. For all other data in the CRF, it must be possible to verify these against source documents.

Computerized data controls will be performed as well and may raise queries where there are inconsistencies. Investigator will be then requested to answer queries as soon as possible.

14. Data Management

The subjects will be identified by subject number, initials, site, and trial identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.

Electronic data transfer of any CRF or subject related data must be approved by the responsible Data Management Unit(s). In cases where data is transferred via non-secure electronic networks, data must be primarily encrypted.

15. Statistics

15.1 Analysis sets (rules for statistical population definition)

The intent-to-treat (ITT) efficacy population will be comprised of 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) efficacy population will be comprised of all patients from the ITT population without major protocol deviation that have received trial product and have completed at least one course of treatment.

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

Patients without progression or death will be included in the efficacy population with a time interval that is right censored.

The responsibility for excluding patients from the analysis will be a joint decision by Sponsor, 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.

15.2 Sample size calculation

The sample size calculation is based on the original primary efficacy endpoint (PFS). We assumed 75% improvement in median PFS in the L-asparaginase (GRASPA) plus low-dose cytarabine group compare to median PFS in the low-dose cytarabine group (control). An hypothesis of 24 months of accrual time and whole study duration of 48 months is 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 (2 : 1), a total of 117 patients should be enrolled to observe 117 events (78 in the L-asparaginase (GRASPA) plus low-dose cytarabine and 39 in the low-dose cytarabine group).

The study size had been increased to 123 patients (41 patients in Arm A and 82 patients in Arm B) in order to incorporate an interim analysis for futility. This interim analysis however will not now be undertaken.

15.3 Statistical methods

A statistical analysis plan (SAP) will be prepared by the CRO and validated by the sponsor. Statistical analyses will be performed with SAS® version 9.2 or higher (SAS institute, North Carolina, USA).
A primary report will be delivered after 12-months follow-up of last patient included. An addendum on 24-months follow-up period will be added for the final report.

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) and depending on the number of missing/invalid data, a data replacement according to the Last Observation Carried Forward method will be performed as a sensitivity analysis.

Missing days and/or months for dates pertaining to events far before the initiation of the study will be replaced by 15 and/or June respectively for time calculations purposes.
Other conventions may be specified in the study statistical analysis plan.

15.3.1 Primary endpoint analysis

The primary endpoint will be analyzed based on the ITT population. Efficacy data will also be analyzed on the Per-Protocol population to assess sensitivity of results to protocol compliance.

The primary objective of the trial is to estimate whether GRASPA plus low-dose cytarabine is more promising than low-dose cytarabine alone with respect to OS in subjects 65-85 years old with newly diagnosed AML unfit for intensive chemotherapy. OS will be calculated from date of randomization to date of death (or censoring).

OS will be summarized using Kaplan-Meier methods. The analysis of OS, will be performed using a stratified log-rank test (stratification factor PS (0, 1 vs 2) to compare treatment groups).

Hypothesis testing will be based on the following relations:

H0 : $\theta = -\log(\lambda) = 0$ and the alternative hypothesis will be H1 : $\theta = \theta 1 > 0$ where λ is the hazard ratio (HR) between the GRASPA plus low-dose cytarabine and the low-dose cytarabine alone groups. In our case (assumption for the median survival times of 2 months and 3.5 months for low-dose cytarabine alone and GRASPA plus low-dose cytarabine respectively) this will mean that H1 : $\theta = -\log(0.5714) = 0.5597$.

A secondary analysis will be performed using Cox's proportional hazards regression model, allowing for the effect of treatment and prognostic factors (ECOG, age and cytogenetic group). For the main criterion of efficacy the significance level will be 0.05 using a two-sided test.

The primary analysis for OS will take place once all patients have completed 12 months in the study. It should be noted however that the study is not powered explicitly for OS and statistical significance in favor of GRASPA plus low-dose cytarabine is not anticipated. 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.

15.3.2 Interim analysis

There will be no interim analysis.

15.3.3 Secondary endpoint analysis

Efficacy endpoints

All efficacy secondary endpoints will be analyzed in the ITT and PP populations.

Progression-free survival (PFS) will be analyzed as a secondary criterion of efficacy. PFS will be defined as the time from date of randomization and resistant disease or relapse or death 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 (i.e. their status must be known at the censored date and should not be lost to follow up or unknown). PFS will be analyzed at the time of final analysis using a stratified log-rank test (stratification factor, PS). A Cox model will also be used to test the effect of treatment and will include terms for prognostic factors (PS, age and cytogenetic group).

The analysis of objective response rate (i.e. CR or PR) will be performed using logistic regression including treatment factor and PS. Secondary analysis will be performed where the logistic regression model will allow for the effect of treatment, and will also include prognostic factors as for OS and PFS. Percentage of patients with CR, CRi, CRp and PR will be calculated and associated exact 95% CIs will be presented by treatment group. Median duration of response from onset of response (RFS) will be calculated and summarized by treatment group for the subset of responders.

Absolute and relative change from baseline EORTC quality of life (QoL) questionnaire scores will be described in each treatment group. EORTC QoL questionnaire scores will be compared across time in each treatment group using a mixed model for repeated data.

Time until QoL deterioration will be defined as a decrease in QoL score from baseline without any return to a better state during the study. A threshold of 10% decrease in QoL score will be primarily used. Other thresholds may be used as exploratory analyses. Death will also be considered as a QoL deterioration. Time to QoL deterioration will be summarized using Kaplan-Meier methods and will be compared between treatment groups using a stratified log-rank test (stratification factor, PS).

Percentage of patients who need transfusions (red blood cells and/or platelets), mean number of transfusions by patient and mean number of hospitalizations (more than over 24 hours) required during the study will be described with their corresponding 95% CI in each treatment group.

The primary analysis of the main secondary endpoints for efficacy will take place once all patients have completed 12 months in the study as for the primary endpoint. A further supportive set of analyses will take place following completion of 24 months in the study for all patients.

Safety endpoints

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.

Vital signs and laboratory data will be listed and summarized by actual treatment group based on the safety analysis set. Summary of absolute values over time (one table per vital sign/laboratory parameter) and summary of change from baseline values over time (one table per vital sign/laboratory parameter) will be presented. Patients with vital sign/laboratory values of NCI-CTCAE grade 3 or 4 will be identified.

Pharmacokinetics and immunogenicity will only be assessed on the subgroup of subjects having received GRASPA. Samples for amino acids (asparagine, aspartate, glutamine, and glutamate), and whole blood asparaginase will be taken on Days 11, 13, 18 and 27 of the first two cycles of treatment after amendment implementation. Summary of absolute values over time (one table per parameter) and summary of change from baseline values over time (one table per parameter) will be presented separately for patients recruited before and after the protocol amendment. Whole blood L-asparaginase concentrations from this study will be evaluated using a population pharmacokinetic analysis. Prior to the 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.

16. Ethics and regulatory

The Sponsor and investigators must ensure that the study will be carried out in compliance with the protocol, the principles of ICH GCP and the declaration of Helsinki (appendix 9)

16.1 Independent Ethics committees and regulatory authorities submissions

The Sponsor must submit the protocol and appropriate related materials to Ethic Committee(s) and local Competent Authority according to national legislation. Approval from Ethic committee(s) and competent authorities must be granted prior to the study start.

Any substantial amendment to the protocols will be implemented only after approval of these bodies as well.

Regulatory Authorities will be provided with amendments if any, reports on SAEs, and the Integrated Clinical Trial Report according to national regulations.

16.2 Informed Consent Form of trial subjects

Prior to any trial related activity, the Investigator must give the subject (and/or parents or the subject's legally acceptable representative, if applicable) oral and written information about the trial in a form that the subject can read and understand. This form (see Appendix 10: Patient information sheet - Informed Consent Form) aims at detailing study purpose and methods, background and present knowledge of investigational product, benefits, risks, study assessments including full exams performed, personal data access and treatment, subject's right regarding the possibility, at any time, to withdraw his/her consent for participating in the study, without penalty about treatment he would beneficiate afterwards. Subject must be given sufficient time and opportunity to inquire about details, discuss and decide on his/her participation with the investigator concerned.

A voluntary, signed and dated Informed Consent Form must be obtained from the subject before any specific study screening procedure. Alternatively, the consent can be given orally in the presence of an independent witness who will sign the Informed Consent Form. Healthy subjects must always give signed informed consent. The written informed consent must be signed and dated by the person who conducted the informed consent procedure. The original will be filed in Investigator Study File; a copy of the document will be retained by the subject and another one will be collected by the sponsor (Assurance Quality Department) in secured sleeves.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained.

16.3 Source data

Source data mean data the patient medical file contains, including but not limited to: medical history, concomitant medication (received or withdrawn), clinical assessment, vital signs, any original document such as exam reports, laboratory results, consultant letters and correspondence, nurse's notes…

NB: patient's involvement in the study should be clearly documented in his/her medical file; details should include the study protocol number, the hospital/unit code, the patient's identification and randomization number, the patient's consent to take part in the study (with the date of consent), the dates of all study visits.

Such essential documents must be retained by the investigator in accordance with local regulations (see section 20).

Any or part of data source may be recorded in the CRF (see section 12) for study purpose.

16.4 Access to source data

By signing Informed consent Form, the subject agrees that investigators, monitors and all mandated staff have access to his/her personal data to ensure control and quality of data recorded for corresponding study purposes only.

By agreeing to participate in this clinical trial, the investigator agrees to give full and direct access to sponsor, or mandated staff or health authorities to source data for each patient enrolled, in the course of trial related monitoring, audits, IRB/IEC review and regulatory inspection.

Subject may accede to his/her personal data on written request, for information or corrective purpose.

16.5 Source data confidentiality

Investigators and any study team member who have patient data access are subject to professional secrecy.

Source data recorded will be treated on an anonymous way. For this purpose, complete patient first name and last name will not appear in any study record. Data will be related to subject identified by a single number (see section 7.3 for assignment to subject number).

In countries where it is authorized by local regulations, patients may also be identified with initials (first two letters from last name followed by first letter from first name).

In accordance with legal requirements, anyone having direct access to source data must respect data confidentiality and follow any specific procedure to warrant subject anonymity on documents that could be forwarded to the sponsor.

16.6 Source data electronic management

Data from subjects enrolled will be encrypted so as to warrant subject anonymity, in accordance with laws regarding electronic data treatment.

17. Duration and termination of trial

17.1 Trial duration

Trial assessment will last 24 months for each patient.

Patient treatment will consist in successive 28-days blocks of low intensive chemotherapy (number of blocks depends on treatment response).

Investigational product is given/ provided during the whole period the patient is under low intensive chemotherapy.

Recruitment period planed: 3 years

Expected start date: Q1 2013

Expected completion date: Q1 2018

17.2 Trial location

This trial will involve European Health Care Centers.

The sites will be chosen according to their experience in conducting clinical trial and handling patients with AML.

Additional countries could be opened if the medical practice allows the protocol to be followed.

17.3 Trial termination

Trial termination is defined as last patient last visit.

The Sponsor or the Investigator may decide to stop the trial or part of the trial at any time. In this case agreement on procedures to be followed must be obtained.

If a trial is prematurely terminated or suspended please refer also to section 11.5.

18. Protocol deviations

Protocol deviations should not occur. If deviations occur, the Investigator must inform the Monitor, for implications of the deviation review and discussion. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the subject and/or the trial. The documentation must be kept in Investigator Study File and the Sponsor File, and will be treated as per sponsor procedure.

19. Audits and Inspections

Data obtained in this trial as well as all or part of trial process may be audited or inspected by an independent qualified person mandated by ERYTECH Pharma or the Competent Authority.

20. Retention of clinical trial documentation

During the study, the Investigator must maintain accurate and updated trial records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Trial records concerned are patient clinical source documents and Investigator Study File with required documents.

Regarding patient clinical source documents, subject notes must be kept for the maximum time period permitted by the hospital, institution or private practice. Other source documents, copies of patients CRF and the Investigator's Trial File must be retained for at least 15 years after study completion or longer in accordance with local regulations.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and ERYTECH Pharma, to store these in a secure archive facility outside the site; they can therefore be returned to the Investigator in the event of a regulatory audit.

The Investigator should not destroy any documents without prior permission from ERYTECH Pharma, including when the 15-year archiving period is over.

In case the documentation should be relocated, or if investigator is to be retired, ERYTECH Pharma should be notified regarding new location of the files or new responsible person for archiving.

ERYTECH Pharma, as the owner of the study data, will maintain the documentation pertaining to the trial as long as the product is on the market and for a minimum of 15 years after the trial completion, or in accordance with national regulations, if they require a longer retention period.

21. Responsibilities

The Investigator is accountable for the conduct of the trial at his/her site. If any responsibility is delegated, the Investigator should maintain a list of appropriate qualified persons to whom he/she has delegated relevant trial related tasks.

21.1 Trial execution

ERYTECH Pharma is responsible for trial execution.

Some responsibility may be transferred at a later stage. If applicable, the transfer of responsibility will be documented.

21.2 Central laboratory

Regarding analyses performed in Central Laboratories, please see details in Appendix 3: Samples preparation for centralized analyses). The conditions for preparation, storage and shipment of blood samples from the sites to the Central Laboratory will be detailed in a "Laboratory Manual" that will be provided to all the sites before trial starting.

22. Financing and Insurance

In accordance with the national law into force, a contract of insurance is subscribed by the Sponsor near the company HDI GERLING Industrie Versicherungs-AG, Riethorst 2 – D 30659 Hannover, (contract no 01005345/14058).

23. Trial report and publication policy

All information supplied by ERYTECH Pharma in connection with this trial shall remain the sole property of ERYTECH Pharma and is to be considered as confidential information. No confidential information shall be disclosed to others without prior written consent from ERYTECH Pharma and shall not be used except in the performance of this trial.

A Final Study Report will be prepared under the responsibility and supervision of ERYTECH Pharma. It will be signed by the Principal Investigator, indicating agreement with the analyses, results and conclusions of the report.

The information obtained during this trial is considered confidential and will be used by ERYTECH Pharma for registration purposes and for the clinical development of the drug.

The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the drug, if deemed necessary by ERYTECH Pharma.

No permission to publish will be granted to any of the providers involved in the trial.

24. Quality assurance statement

This study will be conducted in compliance with the protocol, current GCP rules and the applicable regulatory requirements.

Quality control will be carried out as per standard operating procedures in force by ERYTECH Pharma.

The amended protocol has been audited by ERYTECH Pharma Quality Assurance Department.

Cécile Lacroix *ERYTECH Pharma* *Quality Assurance Manager*	Date

24. Quality assurance statement

This study will be conducted in compliance with the protocol, current GCP rules and the applicable regulatory requirements.
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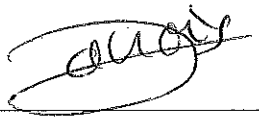

04 - 11 - 2015

Cécile Lacroix
ERYTECH Pharma
Quality Assurance Manager

Date

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26. Appendices

Appendix 1: SPC Cytarabine Hospira UK (ENG) and SPC Aracytine (FRA)
Appendix 2: Inclusion and Randomization Process
Appendix 3: Samples preparation for centralized analyses
Appendix 4: EORTC QLQ-C30 version 3 Quality of life questionnaire
Appendix 5: Prescription of GRASPA
Appendix 6: GRASPA Shipment and Administration Form with GRASPA guidelines
Appendix 7: SAE report form
Appendix 8: Procedure to follow in case of an immediate event linked to red blood cells transfusion
Appendix 9: Declaration of Helsinki
Appendix 10: Patient information sheet - Informed Consent Form
Appendix 11: History of changes

Appendix 1: Summary of Product Characteristics: SPC Cytarabine Hospira UK (ENG) and SPC Aracytine Pfizer (FRA)

RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT

ANSM - Mis à jour le : 26/06/2015

1. DENOMINATION DU MEDICAMENT

ARACYTINE 100 mg, poudre et solvant pour solution injectable

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Composition de la poudre
Cytarabine ..... 100,00 mg

Pour un flacon de 100 mg de poudre.

Pour la liste complète des excipients, voir rubrique 6.1.

3. FORME PHARMACEUTIQUE

Poudre et solvant pour solution injectable.

4. DONNEES CLINIQUES

4.1. Indications thérapeutiques

- Leucémies aiguës myéloblastiques de l'adulte et de l'enfant.

- Leucémies aiguës lymphoblastiques et localisation méningée de la maladie.

- Transformation aiguë des leucémies myéloïdes chroniques et des myélodysplasies.

4.2. Posologie et mode d'administration

La posologie et le mode d'administration varient selon le protocole d'associations thérapeutiques utilisées.

Posologie

Différents schémas thérapeutiques utilisant la cytarabine ont été proposés :
Leucémies aiguës myéloblastiques et transformation aiguë des leucémies myéloïdes chroniques et des myélodysplasies :
Les posologies données en mg/m^2 de surface corporelle sont utilisables chez l'adulte et l'enfant.
Induction :
Chimiothérapie d'association (toujours avec une anthracycline, parfois avec d'autres anti-néoplasiques) :
100 mg/m^2 /j pendant 7 à 10 jours
Ou
200 mg/m^2 /j pendant 5 à 7 jours.
Une deuxième cure peut être administrée en cas d'échec de la première.
Entretien et consolidation :
Une consolidation peut être faite avec le même protocole de chimiothérapie que celui qui a permis d'obtenir la rémission. La cytarabine peut être administrée à des doses inférieures, seule ou en association avec d'autres antinéoplasiques, par cures espacées de 4 à 6 semaines lors des traitements d'entretien.
Dans les traitements d'entretien, la voie sous-cutanée peut être utilisée : 20 mg/m^2 /jour, administrés en 1 ou 2 injections pendant 5 à 10 jours.
Leucémies aiguës lymphoblastiques :
Traitement d'induction et d'entretien :

Les protocoles utilisés sont assez voisins de ceux du traitement des leucémies aiguës myéloïdes.
Ils utilisent des associations comprenant principalement : cytarabine-vincristine-prednisolone.
Traitement des localisations méningées par voie intrathécale :
A titre préventif, on propose la cytarabine : 20 mg/m^2, parfois associée au méthotrexate et à l'hydrocortisone.
Pour l'enfant de moins de 3 ans, la dose de cytarabine est de 30 mg/m^2.
A titre curatif, on utilise habituellement la dose de 20 mg/m^2 une à deux fois par semaine.
L'alcool benzylique ne doit pas être utilisé pour la reconstitution de la solution dans le cas d'une administration intrathécale.

ADAPTATION POSOLOGIQUE :

- La fréquence des cures est fonction du résultat thérapeutique et de la toxicité hématologique et extra-hématologique.

- Des contrôles répétés, sanguins et médullaires devront être effectués, surtout en début de traitement. Les fonctions hépatiques et rénales seront également surveillées.

- L'adaptation de la posologie se fait en fonction des résultats des examens sanguins et médullaires (myélogramme).

- Habituellement le traitement est interrompu si :

    - Les plaquettes sont inférieures à 50 000/mm^3,

    - Les polynucléaires neutrophiles sont inférieurs à 1 000/mm^3.

- La reprise du traitement se fait dès que les chiffres des numérations le permettent et dès que les cellules blastiques réapparaissent dans le sang ou dans la moelle. Le fait d'attendre la normalisation de la numération pour reprendre le traitement est préjudiciable au contrôle ultérieur de la maladie.

- Les posologies seront aussi modifiées en cas de phénomènes toxiques autres qu'hématologiques et en cas d'association à d'autres agents chimiothérapiques.

MODE D'ADMINISTRATION
La cytarabine peut être utilisée par différentes voies d'administration.

- Voie intraveineuse en injection directe ou en perfusion continue : lorsque la cytarabine est administrée rapidement, les doses injectées peuvent être plus importantes que celles qui le seraient par perfusion lente; ceci est dû à l'inactivation rapide du produit et à sa durée de contact très courte avec les cellules néoplasiques et normales sensibles.

- Voie sous-cutanée : la cytarabine est particulièrement bien tolérée. On observe très rarement douleur et inflammation au point d'injection.

- Voie intrathécale : la cytarabine est utilisée dans le traitement préventif et curatif des localisations méningées des leucémies aiguës lymphoblastiques de l'enfant.

En cas d'utilisation par voie intrathécale, la reconstitution se fait avec du L.C.R. autologue ou avec une solution de chlorure de sodium isotonique ; l'utilisation doit être immédiate.
L'alcool benzylique ne doit pas être utilisé pour la reconstitution de la solution dans le cas d'une administration intrathécale.
Quelle que soit la voie d'administration, l'expérience clinique acquise suggère que les résultats obtenus par la cytarabine dépendent étroitement des modifications posologiques de façon à détruire le plus de cellules blastiques avec le moins d'effet toxique. Une association polychimiothérapique entraîne des modifications de posologie pour chacun des constituants du protocole.

Modalités de manipulation :

La préparation des solutions injectables de cytotoxiques doit être obligatoirement réalisée par un personnel spécialisé et entraîné ayant une connaissance des médicaments utilisés, dans des conditions assurant la protection de l'environnement et surtout la protection du personnel qui manipule. Elle nécessite un local de préparation réservé à cet usage. Il est interdit de fumer, de manger, de boire dans ce local. Les manipulateurs doivent disposer d'un ensemble de matériel approprié à la manipulation, notamment blouses à manches longues, masques de protection, calot, lunettes de protection, gants à usage unique stériles, champs de protection du plan de travail, conteneurs et sacs de collecte des déchets. Les excréta et les vomissures doivent être manipulés avec précaution. Les femmes enceintes doivent être averties et éviter la manipulation des cytotoxiques. Tout contenant cassé doit être traité avec les mêmes précautions et considéré comme un déchet contaminé. L'élimination des déchets contaminés se fait par incinération dans des conteneurs rigides étiquetés à cet effet.
Ces dispositions peuvent être envisagées dans le cadre du réseau de cancérologie (circulaire DGS/DH/98 n°98/188 du 24 mars 1998) en collaboration avec toute structure adaptée et remplissant les conditions requises.
Instruction pour une ouverture correcte des ampoules :
Important : l'ampoule est prélimée en un point de l'étranglement. La tâche colorée sur l'olive permet l'orientation de celle-ci (figure 1). Saisir l'ampoule, le point coloré dirigé vers soi, l'ampoule s'ouvre facilement en plaçant le pouce sur le point coloré et en exerçant une légère flexion du haut vers le bas (figure 2). Ne pas ouvrir l'ampoule au niveau du trait.

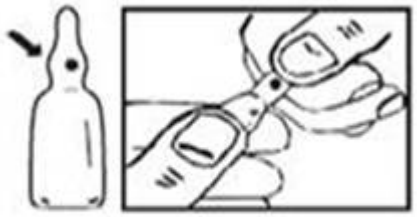


Figure 1

Figure 2

4.3. Contre-indications

- Hypersensibilité à la cytarabine.

- Celles communes à toute thérapeutique cytotoxique.

- Aplasie médullaire préexistante.

- Encéphalopathies dégénératives et toxiques, notamment après emploi du méthotrexate ou de traitement par les radiations ionisantes.

- Patients avec une infection méningée évolutive.

- Allaitement (voir rubrique 4.6).

- Association avec le vaccin antiamarile (fièvre jaune) (voir rubrique 4.5).

- Le solvant à base d'alcool benzylique ne doit pas être utilisé pour la reconstitution de la solution dans le cas d'une administration intrathécale. Dans les autres cas, la solution reconstituée avec ce solvant est contre-indiquée chez les nouveau-nés.

4.4. Mises en garde spéciales et précautions d'emploi

La cytarabine doit être administrée sous stricte surveillance médicale en particulier au cours du traitement d'induction : on pratiquera de façon répétée une numération de la formule sanguine, examens médullaires (myélogramme) afin d'apprécier les résultats thérapeutiques et la toxicité hématologique du traitement.
La cytarabine est un puissant myélosuppresseur : Elle peut entrainer une hypoplasie ou une aplasie médullaire dont la sévérité dépend de la dose administrée et du schéma thérapeutique utilisé.
Insuffisance médullaire préexistante : la cytarabine peut être administrée en cas de nécessité absolue. Le traitement doit dans ce cas être initié avec prudence.
Les patients recevant ce traitement doivent être placés sous surveillance médicale stricte.
Pendant la phase d'induction une numération des globules blancs et des plaquettes doit être réalisée quotidiennement. Des examens médullaires doivent être réalisés fréquemment une fois que les cellules blastiques ont disparu du sang périphérique.
Il conviendra de considérer la possibilité de suspendre ou de modifier le traitement lorsque l'insuffisance médullaire médicamenteuse entraine une réduction du nombre de plaquettes à moins de 50 000 ou de polynucléaires neutrophiles à moins de 1000/mm^3. Il se peut que le nombre d'éléments figurés continue à diminuer après l'arrêt du traitement pour atteindre les valeurs les plus basses après une période sans traitement de 12 à 24 jours. Si cela est indiqué, la reprise du traitement peut se faire lorsque des signes nets de réparation médullaire apparaissent.
Un équipement spécial doit être disponible afin de pouvoir gérer les complications, potentiellement fatales de l'insuffisance médullaire (infections résultant d'une granulopénie et autre diminution des défenses de l'organisme, hémorragies secondaires à la thrombopénie).
On surveillera les fonctions hépatiques et rénales. Les patients ayant une insuffisance hépatique ou rénale présentent un risque plus important de toxicité sur le système nerveux central après administration de fortes doses de cytarabine. Il faudra donc utiliser le produit avec précaution en réduisant les doses chez les patients atteints d'insuffisance hépatique et rénale.
Syndrome de lyse tumorale : Comme toute chimiothérapie antileucémique, la cytarabine induit une hyperuricémie secondaire à la lyse cellulaire : on surveillera le taux d'acide urique pendant le traitement et on préviendra l'hyperuricémie.
Les patients recevant des doses élevées de cytarabine doivent être suivis afin de détecter des signes de neuropathie, car il peut être nécessaire de modifier le schéma d'administration et les doses pour éviter des troubles neurologiques irréversibles (voir rubrique. 4.8).
La vaccination avec un vaccin vivant doit être évitée chez les patients recevant de la cytarabine (voir rubrique 4.5).
L'association de ce médicament est déconseillée avec la phénytoïne (et par extrapolation la fosphénytoïne) (voir rubrique 4.5).

<u>Femmes en âge de procréer traitées (voir rubrique 4.6)</u> :

Les femmes en âge de procréer traitées par la cytarabine doivent utiliser un moyen de contraception efficace au cours du traitement et un mois après la fin du traitement.

<u>Hommes traités (voir rubrique 4.6)</u> :

Il est souhaitable que les hommes traités par la cytarabine ou leur partenaire utilisent une méthode contraceptive de manière à éviter une conception pendant le traitement du patient et dans les 3 mois suivant la fin du traitement.
Les patients traités doivent être avertis de la nécessité de consulter en vue d'une conservation de sperme préalablement au traitement, en raison de la possibilité d'atteinte de la fertilité.
Une ampoule de solvant de 5 ml contient 47,25 mg d'alcool benzylique.
Ce solvant ne doit pas être utilisé pour la reconstitution de la solution dans le cas d'une administration intrathécale.
Dans les autres cas, la solution reconstituée avec ce solvant peut provoquer des réactions toxiques et des réactions de type anaphylactoïde chez les nourrissons et les enfants jusqu'à 3 ans.
Voie intrathécale : La cytarabine, lorsqu'elle est administrée par voie intrathécale, peut être associée à des nausées, des vomissements et à une grave toxicité du système nerveux central qui peut aboutir à un déficit permanent, incluant une cécité et d'autres toxicités neurologiques.
Il est recommandé de ne pas dépasser la dose individuelle validée et d'être très prudent chez les patients ayant déjà reçu un traitement radiothérapique ou intrathécal. Voir rubrique 4.8.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

Interactions médicamenteuses :
En raison de l'augmentation du risque thrombotique lors des affections tumorales, le recours à un traitement anticoagulant est fréquent. La grande variabilité de la coagulabilité au cours de ces affections, à laquelle s'ajoute l'éventualité d'une interaction entre les anticoagulants oraux et la chimiothérapie anticancéreuse, impose, s'il est décidé de traiter le patient par anticoagulants oraux, d'augmenter la fréquence des contrôles de l'INR (acénocoumarol, fluindione, phénindione, tioclomarol, warfarine).
Interactions communes à tous les cytotoxiques :

Association contre-indiquée (voir rubrique 4.3) :

+ **Vaccin antiamarile (fièvre jaune) :** risque de maladie vaccinale généralisée mortelle.

Associations déconseillées (voir rubrique 4.4) :

+ **Phénytoïne (et, par extrapolation, fosphénytoïne) :** risque de survenue de convulsions par diminution de l'absorption digestive de la seule phénytoïne par le cytotoxique, ou bien risque de majoration de la toxicité ou de perte d'efficacité du cytotoxique par augmentation de son métabolisme hépatique par la phénytoïne ou la fosphénytoïne.
+ **Vaccins vivants atténués (sauf antiamarile) :** risque de maladie vaccinale généralisée éventuellement mortelle. Ce risque est majoré chez les sujets déjà immunodéprimés par la maladie sous-jacente.
  Utiliser un vaccin inactivé lorsqu'il existe (poliomyélite).

Associations faisant l'objet de précautions d'emploi :

+ **Antivitamines K :**
  Augmentation du risque thrombotique et hémorragique au cours des affections tumorales. De surcroît, possible interaction entre les AVK et la chimiothérapie.
  Contrôle plus fréquent de l'INR.

Association à prendre en compte :

+ **Immunosuppresseurs :** immunodépression excessive avec risque de syndrome lymphoprolifératif.

4.6. Grossesse et allaitement

Grossesse

Les femmes en âge de procréer traitées par la cytarabine doivent utiliser un moyen de contraception efficace au cours du traitement et un mois après la fin du traitement.
Compte tenu des données disponibles, la cytarabine ne sera administrée pendant la grossesse que si la pathologie met en jeu le pronostic vital de la mère. En effet, les études sur les fonctions de 7/7 reproduction réalisées chez différentes espèces animales ont montré que la cytarabine est embryotoxique et a des effets tératogènes principalement sur le cerveau et le squelette.
Quelques cas de malformations congénitales des membres et de l'oreille externe ont été rapportés lors de l'exposition au premier trimestre de grossesse. En cas d'exposition au premier trimestre, une surveillance échographique orientée est donc recommandée.
Des cas de prématurité ou de retard de croissance intra-utérin ont été signalés.
A la naissance, la survenue d'ictère, d'insuffisance médullaire et d'hyperéosinophilie transitoires a été rapportée. Une surveillance biologique est donc indiquée dans les premières semaines de vie.

Allaitement

L’excrétion de la cytarabine dans le lait maternel n’est pas connue. En raison des effets indésirables potentiellement graves pouvant être entrainés par la cytarabine chez les enfants allaités, la prise de cytarabine doit être contre-indiquée au cours de l’allaitement.

Fertilité

La cytarabine est mutagène et peut induire une atteinte chromosomique des spermatozoïdes.
Les patients traités doivent être avertis de la nécessité de consulter en vue d’une conservation de sperme préalablement au traitement, en raison de la possibilité d’atteinte de la fertilité.
Il est souhaitable que les hommes traités par la cytarabine ou leur partenaire utilisent une méthode contraceptive de manière à éviter une conception pendant le traitement du patient et dans les 3 mois suivant la fin du traitement.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Les effets sur l’aptitude à conduire des véhicules et à utiliser des machines n’ont pas été étudiés. Cependant, sur la base des effets indésirables notifiés, les patients doivent être avertis de ne pas conduire et de ne pas utiliser de machine sans l’avis d’un professionnel de santé.

4.8. Effets indésirables

Investigations :
Dans de rares cas, une hyperuricémie secondaire à la lyse blastique peut être induite par le traitement à la cytarabine; il sera donc nécessaire de surveiller le taux d'acide urique dans le sang et les urines.
Affections cardiaques :
Péricardite.
Des cas de cardiomyopathie pouvant être fatale ont été rapportés suite à l’utilisation expérimentale d’un traitement associant de fortes doses de cytarabine et du cyclophosphamide utilisé dans le cadre de transplantation médullaire.
Affections hématologiques et du système lymphatique :
La cytarabine est un agent antinéoplasique qui entraîne une myélodépression. Son administration entraîne donc une aplasie ou une hypoplasie médullaire responsable d'anémie, granulopénie**,** thrombopénie, mégaloblastose et chute du taux de réticulocytes.
La sévérité de l'aplasie dépend de la dose administrée et du schéma thérapeutique utilisé. En relation avec l'aplasie, des complications hémorragiques ou infectieuses graves peuvent venir compliquer secondairement la cure de chimiothérapie.
Des infections virales, bactériennes, fongiques, parasitaires et saprophytiques peuvent être associées à l’utilisation de la cytarabine seule ou en association avec d’autres médicaments immunosuppresseurs affectant l’immunité cellulaire ou humorale. Ces infections peuvent être légères, mais elles peuvent aussi être graves et parfois fatales.
Affections du système nerveux :
Toxicité neurocérébelleuse pour de fortes doses.
Atteintes cérébelleuses sous forme, au minimum, de dysarthrie et d’un nystagmus, au maximum d’une grande ataxie qui peut être d’apparition retardée et être définitive. Des épisodes de comas, des troubles du comportement et des neuropathies périphériques sensitives et motrices, ont aussi été rapportés. Des cas graves voire létaux ont été observés chez des malades ayant déjà reçu antérieurement d’autres traitements sur le système nerveux central (irradiation encéphalique) : on recommande de ne pas dépasser la dose individuelle validée et on sera très prudent chez les patients ayant déjà reçu un traitement radiothérapique ou intrathécal.
La toxicité neurologique semble en rapport avec un débit rapide d’administration.
Affections oculaires :
Des atteintes réversibles de la cornée et des conjonctivites hémorragiques ont été décrites après utilisation de fortes doses de cytarabine. Ces phénomènes peuvent être prévenus ou diminués par l'instillation d'un collyre contenant des corticoïdes.
Affections respiratoires, thoraciques et médiastinales :
Une toxicité pulmonaire grave, parfois fatale, des syndromes de détresse respiratoire et des œdèmes pulmonaires ont été rapportés après utilisation de fortes doses de cytarabine.

De rares cas de pneumopathies interstitielles ont été rapportés chez des patients traités avec des doses intermédiaires de cytarabine associée ou non à d'autres agents de chimiothérapie, sans que cela ait pu être associé de façon claire à la cytarabine.
Affections gastro-intestinales :
Nausées, vomissements, anorexie sont fréquents avec l'utilisation de la cytarabine, d'autre part risque de stomatite et de mucite. Les nausées et vomissements sont plus fréquents à la suite d'une perfusion rapide. Quelques rares cas d'ulcérations gastro-intestinales sévères avec perforation et péritonite, nécrose intestinale ont été décrits.
Des cas de pancréatite aigüe ont été rapportés chez des patients traités avec de la cytarabine en association avec d'autres médicaments.
Affections des reins et des voies urinaires :
Insuffisances rénales et rétentions urinaires.
Affections de la peau et du tissu sous-cutané :
Rashs cutanés ou dermites exfoliatives.
Alopécie totale.
Ulcérations cutanées.
Troubles généraux et réactions au site d'administration :
Thrombophlébites et cellulites au point d'injection.
Poussées fébriles.
Affections du système immunitaire :
Dans de rares cas : Syndrome cytarabine qui se caractérise par élévation thermique, myalgies, douleurs osseuses accompagnées dans certains cas par des douleurs thoraciques, rashs maculopapuleux, conjonctivite et sensation de malaise général. Ce syndrome survient 6 à 12 heures après l'administration du produit.
Son traitement et sa prévention répondent aux corticoïdes.
Réactions anaphylactiques :
Œdème allergique.
Affections hépato-biliaires :
Abcès hépatique et altération fonctionnelle hépatique avec élévation de la bilirubine.
Ictère.
Affections des organes de reproduction et du sein :
Aménorrhée, azoospermie.
Effets secondaires et toxicité de la voie intrathécale de la cytarabine :
Les effets les plus fréquemment rapportés après administration par voie intrathécale sont des nausées, des vomissements et de la fièvre. Ces réactions sont légères.
Des accidents de neurotoxicité graves dont des paraplégies ont été rapportés lors d'administrations intrathécales combinées avec du méthotrexate et des corticostéroïdes et lors d'association d'injection intrathécale avec une administration systémique de fortes doses de méthotrexate et de cytarabine.
Des cas de leucoencéphalites nécrosantes avec ou sans convulsion ont été rapportés. Certains de ces patients ont aussi été traités par méthotrexate et/ou hydrocortisone par voie intrathécale et par irradiation encéphalique.
Deux cas de cécité ont été décrits chez des sujets mis en rémission après polychimiothérapie intraveineuse et traitement préventif des greffes méningées avec cytarabine intrathécale et radiothérapie de l'encéphale.
Déclaration des effets indésirables suspectés
La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration: Agence nationale de sécurité du médicament et des produits de santé (Ansm) et réseau des Centres Régionaux de Pharmacovigilance www.ansm.sante.fr.

4.9. Surdosage

Il n'existe pas d'antidote spécifique. La dose de 4,5 g/m^2 en perfusion IV d'une heure toutes les 12 heures en 12 doses provoque une toxicité du système nerveux central irréversible et létale.

5. PROPRIETES PHARMACOLOGIQUES

5.1. Propriétés pharmacodynamiques

Classe pharmacothérapeutique : Agents Antinéoplasiques – Antimétabolites – Analogue de la pyrimidine
Code ATC : L01BC01
Antimétabolite spécifique de la phase S du cycle cellulaire (phase de division cellulaire).
La cytotoxicité de la cytarabine dépend de son métabolite actif l'ARA-CTP qui incorporé à l'ADN en bloque la synthèse. La molécule d'ADN comprenant de l'ARA-CTP présente des anomalies structurales aboutissant à des perturbations du métabolisme cellulaire et altérant sa reproduction. La cytotoxicité passerait aussi par une inhibition de l'ADN polymérase et par une action sur le système des kinases.
L'utilisation de hautes doses de cytarabine a montré qu'elles permettent de vaincre la résistance des cellules leucémiques ne répondant plus aux doses conventionnelles du produit.
Plusieurs mécanismes semblent intervenir pour vaincre cette résistance :

- augmentation de la quantité de substrat,

- augmentation du pool intracellulaire d'ARA-CTP: il existe une corrélation positive entre la rétention intracellulaire d'ARA-CTP et le pourcentage de cellules en phase S.

5.2. Propriétés pharmacocinétiques

Pharmacocinétique de la cytarabine utilisée à haute dose : la pharmacocinétique de la cytarabine à haute dose (H.D ARA C) est bicompartimentale (modèle à 2 compartiments).
Après administration intraveineuse d'une dose de 2 à 3 g/m² toutes les 12 heures en perfusion d'une heure sur 5 à 6 jours (10 à 12 doses), les concentrations plasmatiques en fin de perfusion sont de l'ordre de : 19,96 $\pm$ 8,02 µg/ml et 35 $\pm$ 2,8 µg/ml. Les concentrations plasmatiques décroissent à l'arrêt de la perfusion, selon une courbe biexponentielle. Six heures après la fin de la perfusion les concentrations obtenues correspondent à celles mesurées au "steady-state" après une perfusion continue de 24 heures de 100 mg / m² de cytarabine.
Par comparaison avec la cinétique de la cytarabine à dose conventionnelle, les hautes doses produisent un pic 200 fois supérieur.
De même le pic d'apparition d'ARA-U métabolite inactif est retardé avec les hautes doses puisqu'il n'apparaît qu'au bout de 15 minutes.
Aux doses conventionnelles :

- la T ½ est de l'ordre de quelques minutes (10 en moyenne),

- la T ½ B est de l'ordre de quelques heures (1 à 3).

Liaison aux protéines : 14 % de la cytarabine environ est lié aux protéines plasmatiques.
Clairance rénale plus lente avec les hautes doses, de l'ordre de 232 + 33,4 ml/min/m².
La cytarabine administrée par voie générale (IV) passe la barrière hémato-encéphalique : après une dose de 1 à 3 g/m² en perfusion de 1 à 3 heures, les concentrations dans le liquide céphalo-rachidien sont de l'ordre de 100 à 300 ng/ml.
Le produit diffuse aussi dans la salive, la rate, les reins, le tube digestif, le thymus, la moelle osseuse et les larmes. On ne sait pas si la cytarabine passe dans le lait maternel.
Activation de la cytarabine en ARA-CTP métabolite actif :
Passage de la membrane cellulaire par une diffusion facilitée selon le gradient de concentration à haute concentration, par un mécanisme utilisant un transporteur à faible concentration.
Activation enzymatique par phosphorylations successives : les enzymes qui activent l'ARA-C sont celles qui assurent l'activation du ribonucléoside naturel, la déoxycytidine.
Deux enzymes jouent un rôle important : déoxycytidine kinase (ARA-C $\rightarrow$ ARA-CMP) et déoxycytidilate kinase (ARA-CMP $\rightarrow$ ARA-CDP).
Le métabolite actif formé est l'ARA-CTP (arabinofuranosylcytosine tri-phosphate). La formation de l'ARA-CTP est une condition nécessaire à la cytotoxicité du produit mais n'est semble-t-il pas la seule : d'autres mécanismes interviennent.
Catabolisme :
La cytarabine est dégradée en ARA-U (arabinofuranosyl uracile), métabolite inactif, par la cytidine déaminase, enzyme présente dans de nombreux tissus mais principalement dans le foie et aussi dans

les cellules leucémiques et la moelle. Cette enzyme est la cible de nombreux phénomènes d'activation ou d'inhibition.

5.3. Données de sécurité préclinique

Les études de toxicité chez la souris, le rat et le chien par voie orale, intraveineuse, intrapéritonéale, sous-cutanée et intra-articulaire ont montré que les organes cibles sont : le système hématopoïétique (mégaloblastose, réticulocytopénie, leucopénie, thrombocytopénie, et anémie), le cerveau (destruction des fonctions cérébrales et cérébelleuses) et dans une moindre mesure le foie (élévation modérée des enzymes hépatiques à insuffisance hépatique) et les reins (néphrotoxicité). La sévérité de la toxicité est dose-dépendante. Les autres effets observés sont : une toxicité pulmonaire, gastro-intestinale (diarrhées, ulcérations), cardiomyopathie, des conjonctivites et des rashs cutanés.
Aucune étude de fertilité n'a été réalisée, mais des effets sur la fertilité mâle ont été rapportés chez la souris. La cytarabine est embryotoxique et tératogène (cerveau et squelette) et est responsable d'une toxicité péri- et post-natale chez de nombreuses espèces. Administrée à des rats nouveau-nés à la dose de 4mg/kg/j, la cytarabine a provoqué des retards de développement.
La cytarabine est mutagène et clastogène.
Aucune étude de cancérogenèse n'a été réalisée.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Solvant: alcool benzylique, eau pour préparation injectable.

6.2. Incompatibilités

Il existe une incompatibilité physico-chimique de la cytarabine avec l'héparine, l'insuline, le 5-fluoro-uracile, la nafcilline, l'oxacilline, la pénicilline G, le solu-B (solution injectable de vitamines du groupe B, vitamines C et PP) et l'hémisuccinate de méthylprednisolone.
ARACYTINE ne doit pas être mélangé avec d'autres médicaments à l'exception de ceux mentionnés dans la rubrique 6.6. S'assurer de la compatibilité avant de le mélanger ou de l'associer à toute autre substance.

6.3. Durée de conservation

Avant reconstitution : 5 ans
Après reconstitution : voir rubrique 6.4.

6.4. Précautions particulières de conservation

Après reconstitution: 48 heures à température inférieure à 25°C

6.5. Nature et contenu de l'emballage extérieur

Poudre:
Flacon en verre incolore de type I de 10 ml fermé par un bouchon en caoutchouc bromobutyle.
Solvant:
Ampoule en verre incolore de type I de 5 ml.

6.6. Précautions particulières d'élimination et de manipulation

Ne pas utiliser une solution dans laquelle un léger trouble serait apparu.

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

PFIZER HOLDING FRANCE

23-25, AVENUE DU DOCTEUR LANNELONGUE
75014 PARIS

8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE

- 302 672-1 ou 34009 302 672 1 9 : flacon de 10 ml (verre incolore) de poudre pour solution injectable -ampoule de 5 ml (verre incolore) de solvant, boîte de 1.

- 553 151-2 ou 34009 553 151 2 4 : flacon de 10 ml (verre incolore) de poudre pour solution injectable -ampoule de 5 ml (verre incolore) de solvant, boîte de 25.

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

[à compléter par le titulaire]

10. DATE DE MISE A JOUR DU TEXTE

[à compléter par le titulaire]

11. DOSIMETRIE

Sans objet.

12. INSTRUCTIONS POUR LA PREPARATION DES RADIOPHARMACEUTIQUES

Sans objet.

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I.

SPC Cytarabine - Hospira

1. Name of the medicinal product

Cytarabine 20 mg/ml Injection

2. Qualitative and quantitative composition

Each 1 ml contains 20 mg of cytarabine.

Presentations	100 mg/5 ml	500 mg/25 ml	1 g/50 ml
Amount cytarabine present	100 mg	500 mg	1 g

For excipients see 6.1.

3. Pharmaceutical form

Solution for injection.
Clear, colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Cytarabine may be used alone or in combination with other antineoplastic agents. It is indicated alone or in combination for induction of remission and/or maintainance in patients with acute myeloid leukaemia, acute non-lymphoblastic leukaemias, acute lymphoblastic leukaemias, acute lymphocytic leukaemia, erythroleukaemia, blast crises of chronic myeloid leukaemia, diffuse histiocytic lymphomas (non-hodgkin's lymphomas of high malignancy), meningeal leukaemia and meningeal neoplasms.
Clinicians should refer to the current literature on combination therapy before initiating treatment.

4.2 Posology and method of administration

Cytarabine 20 mg/ml Injection is a ready to use solution and is suitable for intravenous, subcutaneous and intrathecal use.
Cytarabine 20 mg/ml Injection can be diluted with Sterilised Water for Injections BP, Glucose Intravenous Infusion BP or Sodium Chloride Intravenous Infusion BP. Prepared infusions, in the recommended diluents should be used immediately. Alternatively, the diluted infusion fluids may be stored at 2-8°C, protected from light, but portions remaining unused after 24 hours must be discarded.

Remission Induction: Adults

Continuous Dosing: The usual dose in leukaemia, is 2 mg/kg by rapid intravenous injection daily for ten days. If after ten days neither therapeutic response not toxicity has been observed, the dose may be increased to 4 mg/kg until a therapeutic response or toxicity is evident. Daily blood counts should be taken. Almost all patients can be carried to toxicity with these doses.
Alternatively, 0.5 to 1 mg/kg may be infused daily in 1-24 hours for ten days, and then at a rate of 2 mg/kg/day until toxicity is observed. Continue to toxicity or until remission occurs. Results from one hour infusions have been satisfactory in the majority of patients.

Intermittent dosing: Cytarabine may be given as intermittent intravenous doses of 3-5 mg/kg daily, for five consecutive days This course of treatment can be repeated after an interval of 2 to 9 days, and repeated until the therapeutic response or toxicity is exhibited.
Evidence of bone marrow inprovement has been reported to occur 7-64 days days after the beginning of therapy.
In general, if a patient shows neither remission or toxicity after a trial period, then cautiously administered higher doses can be administered. Generally patients tolerate higher doses given by rapid intravenous injection rather than slow infusion.
As a single agent for induction of remissions in patients with acute leukaemia, cytarabine has been given in doses of 200 mg/m^2 by continuous intravenous infusion for five days at approximately 2 week intervals.

Maintainance therapy: To maintain remission, doses of 1 mg/kg may be given intravenously or subcutaneously, once or twice weekly.
Leukaemic Meningitis: Therapy for established meningitis employs a wide variety of dose regimens but a recommended total daily dose not exceeding 100 mg, alternating with methotrexate (given either systemically or intrathecally) is recommended. Cytarabine has been given intrathecally at doses of 10-30 mg/m^2 three times a week until cerebro-spinal fluid findings return to normal.
Myelosuppression, anaemia and thrombocytopenia occur almost to all patients given daily infusions or injections. Myelosuppression is biphasic and nadirs at 7-9 and 15-24 days. Evidence of bone marrow improvement may be expected 7-64 (mean 28) days after the beginning of treatment.
Children: Children appear to tolerate higher doses of cytarabine than adults, and where the range of doses is given, children should receive the higher dose.
Elderly: No data is available to suggest that a change in dose is necessary in the elderly. However, the elderly patient is more susceptable to toxic reactions and therefore particular attention should be paid to drug induced leucopenia, thrombocytopenia and anaemia.

4.3 Contraindications

Known hypersensitivity to cytarabine or to any of the excipients.
Anaemia, leucopenia and thrombocytopenia of non-malignant aetiology (e.g. bone marrow aplasia), unless the benefits outweigh the risk.
Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.
During pregnancy, cytarabine should only be administrated on strict indication, where the benefits of the drug to the mother should be weighed against possible hazards to the fetus.

4.4 Special warnings and precautions for use

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving the drug should be kept under close medical supervision. Leucocyte, and platelet counts should be performed frequently and daily during induction. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood.
Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia).
One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitiation has been reported. This occurred immediately after intravenous cytarabine was administered.
Severe and at times fatal central nervous system (CNS), gastrointestinal (GI) and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental cytarabine dose schedule. These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence; convulsion; severe gastrointestinal ulceration including pneumatosis cysteroides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.
Rarely, neurological effects such as quadriplegia and paralysis have been reported with cytosine arabinoside and have been predominantly associated with intrathecal administration. Isolated cases have also been reported with high intravenous doses during combination chemotherapeutic regimens. Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intravenous cytarabine at conventional doses in combination with other drugs.
Cytarabine has been shown to be mutagenic and carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.
Cytarabine should only be used under the constant supervision by physicians experienced in therapy with cytotoxic agents. Hyperuricaemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored. The physician should be prepared to use such supportive and pharmacological measures as may be necessary to control this problem.
Periodic determinations of renal and hepatic functions and bone marrow should also be performed and the drug should be used with caution in patients with impaired hepatic function.

However, dosage reduction does not appear to be necessary in patients with impaired renal function. The human liver apparently detoxifies a substantial fraction of the administered dose. The drug should be used with caution and at a reduced dose when liver function is poor. Frequent platelet and leucocyte counts are mandatory. Therapy should be suspended or modified when drug-induced bone marrow depression results in a platelet count of less than 50,000 or a polymorphonuclear count of under 1000 per mm^3. Counts may continue to fall after the therapy has been discontinued and may reach lowest values after five to seven days. Therapy may be restarted when the bone marrow appears to be recovering on successive bone marrow studies. Therapy should not wait until the normal blood values are obtained to be re-initiated. If treatment is not resumed before blood values return to normal, the disease can get out of control.
When intravenous doses are given quickly, patients may become nauseated and may vomit for several hours afterwards. The problem tends to be less severe when infused.
Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to nonoperative medical management. Concurrent granulocyte-transfusion should be avoided as severe respiratory insufficiency has been reported.
Immunosuppressant effects/Increased susceptibility to infections
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.
High dose therapy
Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukemia. Patients treated with high doses of cytarabine should be observed for neuropathy since dose adjustments may be needed to avoid irreversible neurologic disorders.
Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome, and pulmonary edema have occurred following high dose schedules with cytarabine therapy.
Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.
The risk of CNS toxicity increases if high dose cytarabine is given in combination with another CNS toxic treatment such as radiation therapy or in patients who have previously had CNS treatment as chemotherapy intrathecally. When given intrathecally, as with any other intrathecal drug, care must be taken with radiotherapy given either during or after treatment; it is well recognised that this can exacerbate the toxicity of radiotherapy.
The safety of the drug has not been established in infants.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac Glycosides

GI absorption of oral digoxin tablets may be substantially reduced in patients receiving combination chemotherapy regimens (including regimens containing cytarabine), possibly as a result of temporary damage to intestinal mucosa caused by the cytotoxic agents. Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. Limited data suggest that the extent of GI absorption of digitoxin is not substantially affected by concomitant administration of combination chemotherapy regimens known to decrease absorption of digoxin. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digitoxin for such patients may be considered as an alternative.

Anti-Infective Agents

One *in vitro* study indicates that cytarabine may antagonise the activity of gentamicin against *Klebsiella pneumoniae*. In patients on cytarabine being treated with gentamicin for a K.pneumoniae infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.
5-Fluorocytosine:
5-Fluorocytosine should not be administered with cytarabine as the therapeutic efficacy of 5-Fluorocytosine has been shown to be abolished during such therapy.
Immunosuppressive Agents:
Due to the immunosuppresive action of cytarabine, viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body, may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

4.6 Pregnancy and lactation

Use in Pregnancy

Cytarabine is teratogenic in some animal species. It should not be used in pregnant women (especially during the first trimester) or in those who may become pregnant, unless the possible benefits outweigh the potential risks. Women who are, or who may become, pregnant during treatment with cytarabine should be informed of the risks.
Men and women have to use effective contraception during and up to 6 months after treatment.

Use in Lactation

It is not known if cytarabine or its metabolite is distributed into breast milk, and it should not be used in mothers who are breastfeeding.
Fertility
Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing cytarabine treatment and their partner should be advised to use a reliable contraceptive method.

4.7 Effects on ability to drive and use machines

No documented effect on ability to drive or operate machinery.
Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

The following adverse events have been reported in association with cytarabine therapy.
Frequencies are defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000), not known (cannot be estimated from the available data).
Undesirable effects from cytarabine are dose-dependent. Most common are gastrointestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

***Infections* and infestations**

Uncommon: Sepsis (immunosuppression)

Neoplasms benign,malignant and unspecified (including cysts and polyps)

Uncommon: Lentigo

Blood and lymphatic system disorders

Common: Anaemia, megaloblastosis, leucopenia, thrombocytopenia.
Not known: Reticulocytopenia.
These appear to be more evident after high doses and continuous infusions; the severity depends on the dose of the drug and schedule of administration

Metabolism and nutrition disorders

Common: Anorexia, hyperuricaemia

Nervous system disorders
Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus
Uncommon: Headache, peripheral neuropathy and paraplegia at intrathecal administration
Not known: Dizziness, neuritis or neural toxicity and pain, neurotoxicity rash
Eye disorders
Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis
Not known: Conjunctivitis
Cardiac disorders
Uncommon: Pericarditis
Very rare: Arrhythmia
Respiratory, thoracic and mediastinal disorders
Uncommon: Pneumonia, dyspnea, sore throat
Gastrointestinal disorders
Common: Dysphagia, abdominal pain, nausea, vomiting, diarrhea, oral/anal inflammation or ulceration
Uncommon: Oesphagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis
Not known: Gastrointestinal haemorrhage
Nausea and vomiting may occur and are generally more frequent following rapid intravenous administration than with continuous intravenous infusion of the drug.
Hepatobiliary disorders
Common: Reversible effects on the liver with increased enzyme levels
Not known: Hepatic dysfunction, jaundice
Skin and subcutaneous tissue disorders
Common: Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia,
Uncommon: skin ulceration, pruritus, burning pain of palms and soles
Very rare: Neutrophilic eccrine hidradenitis
Not known: Rash, freckling, skin bleeding
Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, joint pain
Renal and urinary disorders
Common: Renal impairment, urinary retention
Not known: Renal dysfunction
General disorders and administration site conditions
Common: Fever, thrombophlebitis at the injection site, cellulitis at injection site
Not known: Irritation or sepsis at the injection site, chest pain and mucosal bleeding
A cytarabine syndrome (immunoallergic effect) is characterised by fever, myalgia, bone pain, occasionally chest pain, exanthema, maculopapular rash, conjunctivitis, nausea and malaise. It usually occurs 6-12 hours after administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated. If treatment is effective, therapy with cytarabine may be continued.
Adverse effects due to high dose cytarabine treatment, other than those seen with conventional doses include:
Blood and lymphatic system disorders:
Hematological toxicity has been seen as profound pancytopenia which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.
***Nervous system disorders*:**
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influence like personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, etc. appear in 8-37 % of treated patients. The incidence in

elderly (>55 years) may be even higher. Other predisposing factors are impaired liver and renal function, previous CNS treatment (e.g., radiotherapy) and alcohol abuse. CNS disturbances are in the most cases reversible.
The risk of CNS toxicity increases if the cytarabine treatment - given as high dose i.v.- is combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent
Eye disorders:
Reversible corneal lesion and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation of corticosteroid eye drops.
Gastrointestinal disorders:
Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported. Pancreatitis has also been observed after high-dose therapy.
Hepatobiliary disorders:
Liver abscesses, hepatomegaly and Budd-Chiari-syndrome (hepatic venous thrombosis) have been observed after high-dose therapy.
***Respiratory, thoracic and mediastinal disorders*:**
Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26 % in different publications), since the patients usually have been in relapse where other factors may contribute to this reaction.
Reproductive system and breast disorders
Amenorrhoea and azoospermia.
Others:
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported.
The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis.
One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported (see section 4.4 Special warnings and precautions for use).
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
4.9 Overdose
There is no specific antidote for cytarabine overdose. Cessation of therapy followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required. Twelve doses of 4.5 g/m2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.
Cytarabine may be removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Cytarabine (ARA-C) is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA.
Cytarabine has no effect on non proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.
5.2 Pharmacokinetic properties

Oral administration is ineffective due to rapid deamination in the gut. Cytidine deaminase is concentrated in the liver and intravenous doses show biphasic elimination with half lifes of approximately 10 minutes and 1-3 hours.
After 24 hours 80% of a dose has been eliminated either as the inactive metabolite or as the unchanged cytarabine, mostly in urine but some in bile.
CSF levels of 50% of plasma levels are achieved with intravenous infusion. Intrathecal dosing results in slower elimination (T1/2 2-11 hours).
Cytarabine is rapidly and widely distributed into tissues, crosses the blood brain barrier and also the placenta.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride
Water for Injections

6.2 Incompatibilities

Solutions of cytarabine have been reported to be incompatible with various drugs, i.e. carbenicillin sodium, cephalothin sodium, fluorouracil, gentamicin sulphate, heparin sodium, hydrocortisone sodium succinate, insulin-regular, methylprednisolone sodium succinate, nafacillin sodium, oxacillin sodium, penicillin G sodium. However, the incompatibility depends on several factors (e.g. concentrations of the drug, specific diluents used, resulting pH, temperature). Specialised references should be consulted for specific compatibility information.

6.3 Shelf life

Before use: 12 months.
In use: Chemical and physical in-use stability has been demonstrated for 7 days at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton .

6.5 Nature and contents of container

Clear Type I glass vials, rubber stopper.
Clear Type I Onco-Tain® Vials, rubber stopper.
Pack sizes 5's, 25's and 50's.
Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Hospira UK Ltd
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom.

8. Marketing authorisation number(s)

PL 04515/0040

9. Date of first authorisation/renewal of the authorisation

7th July 1992/10th October 2006

10. Date of revision of the text

June 2015

APPENDIX 2 - INCLUSION AND RANDOMIZATION PROCESS

(NB screening shot are corresponding to protocol version dated 21/01/2013)

Connect to www.graspa-ml.com and choose "patients" section, then "new patient"

Enter patient data selection and validate

PATIENT DATA

Before filling the "Patient data" section, please be sure to enter accurate information (particularly Date of birth).

Patient N°:	1004-07 *(as reference for all further correspondences)*
Patient Initials:	Last name: (2 1st letters) First name: (1st letter)
Date of birth:	
Sex:	Male Female
Date of bone marrow sample for exploratory assessments:	

Validate

Only if authorized according local regulations

Answer inclusion exclusion criteria and validate

RANDOMIZATION / SCREENING FAILURE

Before filling the "Randomization / Screening Failure" section, please be sure to have all required information. Otherwise, you can close this window.

INCLUSION CRITERIA

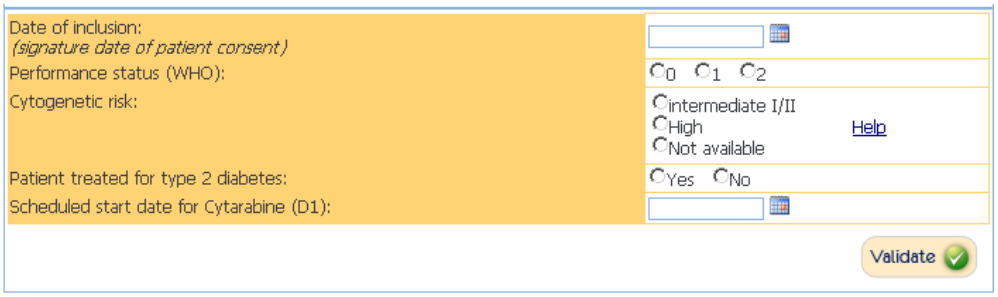
	Yes	No
1- Patient over 65 years old and less than 85 years old		
2- Newly diagnosed Acute Myeloid Leukemia (AML) or post myelodysplastic syndrome diagnosed in the 6 months prior study enrollment		
3- Unfit for intensive chemotherapy (at risk to suffer treatment related pejorative toxicities /early death) or patient unwilling to receive intensive chemotherapy		
4- WHO performance status ≤2 and estimated life expectancy ≥ 3 months		
5- Eligible to receive low-dose cytarabine treatment		
6- Evidence of post-menopausal status for female (absence of menstruation for 12 months)		
7- Subscription to social security insurance		
8- Provision of written Informed Consent		

NON-INCLUSION CRITERIA

	Yes	No
1- Patients with M3 AML of FAB classification (APL, Acute Promyelocytic Leukemia))		
2- Patients with AML involving chromosome 16 abnormalities or translocation (8:21) (CBF-AML)		
3- History of grade 3-4 pancreatitis or grade 3-4 thromboembolic event (according NCI-CTCAE Version 4.0)		
4- Presenting with a general or visceral contraindication including : • Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis. Cardiac insufficiency defined as Left Ventricular Ejection Fraction < 50% of the theoretical value • Plasma creatinine concentration, 2 times greater than the upper limit of laboratory ranges, except if related to AML • AST or ALT levels, 3.5 times greater than the upper limit of laboratory ranges, except if related to AML • Patient presenting evolutive cancer other than AML, except in situ basal-cell carcinoma or in situ cervix cancer • Severe evolutive infection, or, HIV seropositive or, active hepatitis related to B or C viral infection		
5- History of Grade 3 Transfusional incident (life threatening)		
6- Has known or suspected hypersensitivity or intolerance to mannitol, or heparin		
7- Patient presenting contra indication to cytarabine treatment (hypersensitivity to cytarabine, antimitotic treatment, preexisting medullary aplasia, toxic degenerative encephalopathy - especially after methotrexate treatment or ioniding radiations-, yellow fever vaccination)		
8- Participation in an investigational drug study within the 30 days prior to entry		

Validate

Answer question and validate



Confirm or cancel patient randomization (If cancel is chosen, patient will be marked as screening failure)

If confirm is chosen the system display randomization arm on the screen :

Patient 1004-07 is randomized in Arm B - Low-dose Cytarabine + GRASPA® 100 UI/kg.

Randomization number: 0XX

An email confirmation is also sent to the investigator example below :

From : graspa.ml@icta.fr [mailto:graspa.ml@icta.fr]
Sent by : vendredi 29 novembre 2013 17:20
To: Investigator
Subject : GRASPA-ML_Study_Centre 1004_Confirmation of Randomisation - Patient 1004-07

This is the confirmation of the data you have entered into the Interactive Web Response System for the following patient:

Connection to IWRS:
- Date of connection: 29/11/2013

Centre and Patient:
- Centre: 1004 - Investigator
- Patient number: 1004-07
- Sex: Male
- Date of birth: 12/12/1945
- Date of consent form signature: 29/11/2013
- Start Date for Cytarabine (Day 1): 02/12/2013

Randomization:
Your patient 1004-07 has been randomized:

in Arm B – Low-dose Cytarabine + GRASPA® 100 UI/kg
(randomization number 075)

ICTA PM / ERYTECH PHARMA will contact you in the coming days for the arrangement of GRASPA prescription and delivery.

The GRASPA-ML study team

Appendix 3: Samples preparation for centralized analyses

Amino acids: asparagine, aspartate, glutamine, and glutamate - At D11, D13, D18 and D27 of chemotherapy course

Procedure:

One sample of 4mL of blood should be taken and immediately refrigerated (put in an iced water bath)

Centrifuge the blood sample no later than 15 minutes after sampling, at 800-1,000 G and at 4°C for 10 minutes

Harvest the serum and process the sample

Add ≥ 100 µL (1 part) 10% sulfosalicylic acid to ≥ 400 µL (4parts) of serum to precipitate proteins, mix thoroughly (vortex mixer) and centrifuge 5 minutes at 2,500 G at 4°C

Fill the supernatant into a propylene tube and freeze between ≤ -20°C and -80°C, store at this temperature until shipping.

Samples will be transferred on dry ice for analysis to:

SGS Cephac
90, Av. des Hauts de la Chaume BP28
86281 Saint Benoît Cedex, France

Whole blood asparaginase - At D11, D13, D18 and D27 of chemotherapy course

Procedure:

Two sample of 2mL of blood should be taken and freeze between ≤ -20°C and -80°C; store at this temperature until shipping.

Samples will be transferred on dry ice for analysis to:

SGS Cephac
90, Av. des Hauts de la Chaume BP28
86281 Saint Benoît Cedex, France

Immunogenicity: Anti-L-asparaginase antibodies - At D11 each course of chemotherapy, before GRASPA administration

Procedure:

One sample of 2mL of blood should be taken

Centrifuge the blood sample no later than 15 minutes after sampling, at 800-1,000 G and 4°C for 15 minutes

Fill the supernatant into 2 propylene tubes and freeze between ≤ -20°C and -80°C, store at this temperature until shipping.

Samples will be transferred on dry ice for analysis to:

CHU Hôtel Dieu

Laboratoire d'immunologie biologie

9 quai Moncousu

44093 Nantes cedex 1 (France)

Biomarker assessments on bone marrow aspirate of patients.

Procedure

Two Bone marrow samples will be collected as follows:

-2 mL will be collected in EDTA tube (for culturing cells after ficoll separation)

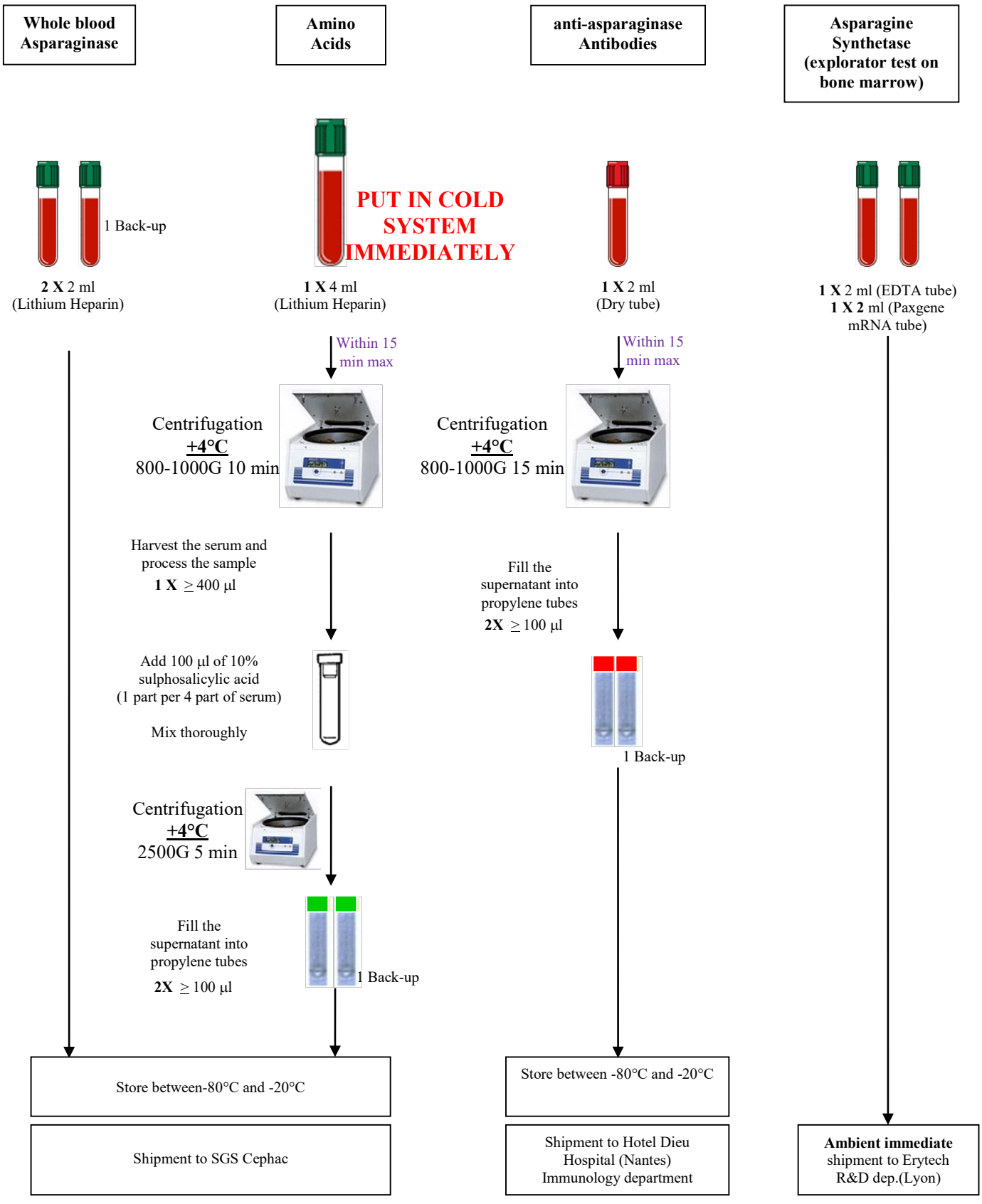
-2 mL will be collected in PAXgene tube (for extraction of RNA)

Patient samples will be transferred (ambient temperature) for analysis to

ERYTECH Pharma – R& D department

60 av Rockefeller, Bât Adenine

69008 Lyon (France)



Fax the Analysis Form to trigger pick-up of samples to ship
Fax No: + 33 (0)1 48 92 22 02 (CEMO)

Dosage and Central Laboratories

Analysis	Reference for measurement	Central Laboratory	Responsible
Amino Acids : Asparagine, Aspartate, Glutamine, Glutamate **Whole blood Asparaginase**	R. Pieters et al, Blood. 2008 Dec 15;112(13):4832-8 Lanvers C, C et al. J. Anal Biochem 2002; 309: 117–126	SGS Cephac 90, Av. des Hauts de la Chaume BP28 86281 Saint Benoît Cedex, France	Patricia Blain - Study Director Phone: +33 5 49 57 50 20 Fax: +33 5 49 57 22 39
Anti-asparaginase Antibodies	B Wang, LJ Hak, MV Relling et al. "Elisa to evaluate plasma anti-asparaginase IgG concentrations in patients with acute lymphoblastic leukemia" J of Immunological Methods 239 (2000) 75-83.	Hôpital Hôtel Dieu Laboratoire d'Immunologie Biologie 9, Quai Moncousu 44093 NANTES Cedex 1 FRANCE	Dr Marie AUDRAIN Tel : +33 (0)2 40 08 40 67 Fax : +33 (0)2 40 08 42 14 marie-audrain@chu-nantes.fr
Asparagine Synthetase exploration/ Biomarker assessments	Erytech study No EGG0-6-05	ERYTECH Pharma 60 Av Rockefeller, bât Adénine 5ème etage 69008 LYON FRANCE	Willy BERLIER Tel : +33(0)4 78 78 15 72 Fax : +33 (0)4 78 78 93 09 wberlier@erytech.com
		MD Anderson Cancer Center 7435 Fannin St, Room 2SCR3.3027 Houston, TX 77054	Philip LORENZI, M.D. Tél: +1 713 792 9999 E-mail: pllorenzi@mdanderson.org

Appendix 4: EORTC-QLQ-C30_V3

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5: Prescription of GRASPA

ETUDE GRASPA-AML2012-01
PRESCRIPTION DE GRASPA®
(eryaspase, dispersion pour perfusion)

IDENTIFICATION DU **CENTRE**	**FAXER A**
IP nom : ……..……..	ERYTECH PHARMA
Adresse du centre : ……..…….	
……. ….	N° FAX : +33(0)4 78 78 93 05
No centre : …….	
N° FAX : …….	

IDENTIFICATION DU PATIENT			
NOM		Monogramme	N° Patient
PRENOM		|__|__| - |__| *Nom Prénom*	|__|__|__|__| - |__|__| *N° Centre N° Patient*
Né(e) le	|__|__| |__|__| |__|__|__|__| *Jour mois année*	Sexe ☐ M ☐ F	
Poids du patient	|__|__|__| Kg		
PRESCRIPTION			
1 poche de GRASPA® compatible sur la base du dossier pré transfusionnel du patient ci-joint		Dose | 1 | 0 | 0 | UI/Kg	
Préciser si caractéristique particulière (ex CMV négatif):			
Date et heure prévue d'administration	|__|__| |__|__| |__|__|__|__| *Jour mois année*	|__|__| H |__|__| mn	

ELEMENTS DU DOSSIER PRE TRANSFUSIONNEL DU PATIENT

Nombre total de pages (comprenant la prescription) : ___ pages

☐ Photocopie de la **carte de groupe** sanguin valide

ATTENTION LE PRODUIT SERA EXPEDIE UNIQUEMENT APRES RECEPTION DES RAI de moins de 72h, A faxer dans les 2 jours précédent l'administration.

En cas de difficulté, appeler immédiatement le Pharmacien ERYTECH Pharma au +33(0)4 78 78 93 04

Date :	Nom du prescripteur :	Signature :

LIVRAISON PHARMACIE

ADRESSE : .....

.....

Tél.: ..... Fax.: .....

CONTACT POUR LA RECEPTION DE GRASPA® **(MENTION OBLIGATOIRE POUR L'EXPEDITION)**
Nom(s), fonction(s): .....

Cadre réservé ERYTECH pour confirmation

Dose | **1** | **0** | **0** | UI/Kg	Dose totale : |__|__|__|__|__| UI	Date Signature :
RAI ATTENDUES POUR LE		

GRASPA-AML2012-01 STUDY
PRESCRIPTION OF GRASPA®
(eryaspase, dispersion for infusion)

SITE IDENTIFICATION PI name: ……..…….. Site address: …… ……. Site No.: ……. FAX No: ……	**TO BE FAXED AT:** ERYTECH PHARMA FAX No : +33(0)4 78 78 93 05

PATIENT IDENTIFICATION			
LAST NAME		Patient Initials	Patient No
FIRST NAME		|__|__| - |__| *Last Name First name*	|__|__|__|__| |__|__| *Site No Pat No*
Date of Birth	|__|__| |__|__| |__|__|__|__| *day month year*	Gender ☐ M ☐ F	
Weight	|__|__|__| Kg		

PRESCRIPTION	
1 compatible bag of GRASPA®, according patient pretransfusionnal status	Dose:| 1 | 0 | 0 | IU/Kg
Precise specific conditions required if any (i.e. CMV negative):	
Administration scheduled on the |__|__| |__|__| |__|__|__|__| *day month year*	at |__|__| h |__|__| min

PATIENT PRETRANSFUSIONNAL STATUS TO BE ATTACHED :

Number of pages (including this prescription sheet) : ___ pages

☐ Completed "BLOOD GROUP FORM"

WARNING: GRASPA® WILL BE SENT ONLY AFTER RECEPTION OF IAST RESULTS LESS THAN 72 H (3 DAYS) PRIOR GRASPA® INFUSION

In case of any difficulty, please contact ERYTECH Pharma Pharmacist Tel No +33(0)4 78 78 93 04

Date :	Investigator Name :	Signature :

DELIVERY ADDRESS

ADDRESS : .....

.....

Tel.: ..... Fax. / Mail.: .....

CONTACT **(MANDATORY FOR SHIPMENT)** Name(s), function(s):

…….. .....

Reserved as per confirmation by ERYTECH

Dose: | 1 | 0 | 0 | IU/Kg	Total Dose : |__|__|__|__|__| IU	Date & Signature :
DATE IAST expected :		

Appendix 6: Transport and injection forms

DOCUMENT DE TRANSPORT ET D'INJECTION DE GRASPA®

ETUDE :
GRASPA-AML2012-01

1- ERYTECH PHARMA - ENVOI DE GRASPA®

ORIGINAL

Date de Prescription	|__|__| |__|__| |__|__|__|__| *jour mois année* Par le Dr/Pr.:	Etiquette Poche avec Identité patient complète
Mise en expédition	|__|__| |__|__| |__|__|__|__| *jour mois année* Par (transporteur) :	

2- PHARMACIE - RECEPTION DE GRASPA®

Date de réception |__|__| |__|__| |__|__|__|__| *jour mois année* **Horaire** |__|__| h |__|__| min

Contrôle qualité de la poche	Conforme	Non Conforme
Identification de patient	☐	☐
Intégrité	☐	☐
Température	☐	☐

Documents et matériel joints	Présent	Absent
Carte de contrôle	☐	☐
Transfuseur double voie (Tubulures de rinçage)	☐	☐
Emballage pour retour de poche	☐	☐

Personne ayant réceptionné le produit (Nom, fonction) : _____

Date et heure de sortie du froid : |__|__| |__|__| |__|__|__|__| *jour mois année* à |__|__| h |__|__| min

par (Nom, fonction) : _____ *Fin de mise à froid, produit à injecter dans **les 6 heures**.*

3- UNITE DE SOIN - ADMINISTRATION DE GRASPA®

Vérification de la prescription : ☐ Oui ☐ Non

Vérification patient/étiquette produit : ☐ Oui ☐ Non

Contrôle ultime au lit (compatible) : ☐ Oui ☐ Non

Date d'administration : |__|__| |__|__| |__|__|__|__| *jour mois année* Début : |__|__| h |__|__| min Fin : |__|__| h |__|__| min

Produit administré : ☐ Oui Totalement ☐ Partiellement ☐ Non

Rinçage des tubulures : ☐ Oui ☐ Non

Cause de non conformité, non injection ou non rinçage

Administration effectuée par :	**Date :** |__|__| |__|__| |__|__|__|__| *jour mois année*	**Signature**

RAPPEL : Retour de la poche à ERYTECH Pharma selon modalités

DOCUMENT COMPLETE A FAXER SANS DELAI AU +33(0)4 78 78 93 05 (Pharmacien ERYTECH Pharma)

ORIGINAL

Etape 1 : RECEPTION DE LA POCHE

- Réception de la poche sous responsabilité pharmaceutique par le Pharmacien de la PUI.
- Effectuer les contrôles à réception selon la rubrique « *Réception de GRASPA®* » au verso de ce document.

Etape 2 : ADMINISTRATION

- Appliquer les règles de vérification ultime (identité, examen du produit, contrôle ultime de compatibilité au lit du patient entre le GRASPA® et le sang du malade)

⚠ Dans le cas où le patient a reçu une transfusion non programmée depuis la prescription de GRASPA®, réaliser avant l'injection une épreuve de compatibilité auprès de votre laboratoire d'immuno-hématologie (segment à disposition sur le produit).
⚠ En cas d'anomalie, le produit ne devra pas être transfusé.

- Transfuser la totalité de la poche
- Rincer les tubulures avec du sérum physiologique (20 à 40 ml de NaCl 0,9%)

Etape 3 : TRACABILITE

- Compléter la section « *Administration de GRASPA®* » au verso de ce document.
- Faxer le Document de transport et d'injection de GRASPA® complété (sections remplies) sans délais au +33 (0)4 78 78 93 05
- Conserver le Document de transport et d'injection de GRASPA® dans le dossier médical du patient

Etape 4 : RETOUR DE LA POCHE (à ERYTECH Pharma)

- Après administration, placer la poche vide dans le sachet prévu à cet effet (ne pas joindre les tubulures)
- Se reporter à la procédure de retour pour effectuer l'enlèvement par le transporteur

GRASPA®
SHIPMENT AND ADMINISTRATION FORM

GRASPA-AML2012-01
English version

1- ERYTECH PHARMA - SHIPMENT OF GRASPA® ORIGINAL

Prescription date	|__|__| |__|__| |__|__|__|__| *day month year* By Dr/Prof.:	label with patient ID
Shipping date	|__|__| |__|__| |__|__|__|__| *day month year* By (carrier) :	

2- RECEPTION OF GRASPA® *To be filled in by the Recipient*

Reception Date |__|__| |__|__| |__|__|__|__| *day month year* **Time** |__|__| h |__|__| min

Quality Control of the bag	Conform	Non Conform	**Related supply**	Present	Absent
Patient Identification	☐	☐			
Integrity	☐	☐	Infusion double line (allowing rinsing)	☐	☐
Temperature	☐	☐	Packaging for bag return	☐	☐

Recipient Name: Signature:

Removing from +2+8°C - Date/Time : |__|__| |__|__| |__|__|__|__| *day month year* at |__|__| h |__|__| min

by (Name) : _____ *To be administered within **6 hours***

3- ADMINISTRATION OF GRASPA®

Consistency with prescription ☐ Yes ☐ No

Check patient identification *vs* label : ☐ Yes ☐ No

Ultimate cross match blood test : ☐ Yes* ☐ No *by (name, title)_____

Administration Date : |__|__| |__|__| |__|__|__|__| *day month year* Start : |__|__| h |__|__| min End : |__|__| h |__|__| min

Product administered : ☐ Yes totally ☐ Partially ☐ Not administered

Infusion line rinsing : ☐ Yes ☐ No

Reason for non-conformity, administration failure, rinsing failure, or any relevant comment

Administration performed by:	**Date :** |__|__| |__|__| |__|__|__|__| *day month year*	**Signature**

PLEASE FAX THIS DOCUMENT COMPLETED TO +33(0)4 78 78 93 05 (ERYTECH Pharmacist)

ORIGINAL

Step 1 : RECEPTION OF GRASPA®

- Under medical responsibility.
- Check items as indicated in section *«Reception of GRASPA®»* in the «GRASPA® shipment and administration form ».

Step 2 : ADMINISTRATION

- Prior to the administration, an ultimate compatibility cross match test should be performed between patient blood and GRASPA® received using segment tube.

⚠ If the patient received a blood transfusion in between GRASPA® prescription and scheduled date of administration of GRASPA®, a new compatibility test should be performed in your local laboratory.
⚠ In case of discrepancy the product must not be administered.

- The entire content of the bag must be infused.
- Rinse the perfusion line with NaCl 0,9% (around 20 to 40 mL).

Step 3 : DOCUMENTATION

- Complete the *«Administration of GRASPA®»* section of the document «GRASPA® shipment and administration form».
- Fax completed «GRASPA® shipment and administration form» form shortly after administration to +33(0)4 78 78 93 05.
- Keep the document «GRASPA® shipment and administration form» completed together with patient medical file.

Step 4 : RETURN OF THE BAG (To ERYTECH Pharma)

- After administration, put the bag of GRASPA® into the supplied packaging for return (please do not insert perfusion lines).
- Follow the instructions to have the package picked.

Schritt 1: ANNAHME DES BEUTELS

ORIGINAL

- Unterliegt ärztlicher Verantwortung.
- Kreuzen Sie die entsprechenden Punkte im Abschnitt *«Reception of GRASPA®»* des Dokuments «GRASPA® shipment and administration form» an.

Schritt 2: VERABREICHUNG

- Vor der Infusion ist mittels Segmentröhrchen und Blutgruppenkarte eine endgültige Kreuzprobe zur Überprüfung der Kompatibilität zwischen Patientenblut und zu verabreichendem GRASPA® durchzuführen.

⚠ Hat der Patient zwischen der Verordnung und der eigentlichen Infusion von GRASPA® eine Bluttransfusion erhalten, muss im Labor Ihrer Einrichtung ein erneuter Kompatibilitätstest durchgeführt werden. Im Falle von abweichenden Ergebnissen darf das Produkt nicht infundiert werden.

- Es muss der gesamte Beutelinhalt infundiert werden.
- Spülen Sie die Perfusionsleitung mit 0,9% iger Kochsalzlösung (etwa 20 bis 40 ml).

Schritt 3: DOKUMENTATION

- Füllen Sie Abschnitt *«Administration of GRASPA®»* im Dokument «GRASPA® shipment and infusion form» aus.
- Faxen Sie das Dokument «GRASPA® shipment and administration form» mit den ausgefüllten Abschnitten zeitnah nach der Infusion an folgende Nummer: +33(0)4 78 78 93 05.
- Bewahren Sie das ausgefüllte Dokument «GRASPA® shipment and administration form» zusammen mit der Krankenakte des Patienten auf.

Schritt 4: RÜCKGABE DES BEUTELS (an ERYTECH Pharma)

- Stecken Sie nach Verabreichung von GRASPA® den Beutel in die mitgelieferte Verpackung für Rücksendungen (legen Sie bitte keine Perfusionsleitungen bei).
- Folgen Sie den Anweisungen, um das Päckchen abholen zu lassen.

Etapa 1: RECEPCIÓN DE LA BOLSA

ORIGINAL

- Recepción de la bolsa bajo responsabilidad médica
- Al recibir el producto, realice los controles de la sección *«Reception of GRASPA®»* en el documento Envío de GRASPA® y Administración «GRASPA® shipment and administration form»

Etapa 2: ADMINISTRACIÓN

- Antes de la administración, una prueba de compatibilidad definitiva debe ser realizada, entre la sangre del paciente y GRASPA® recibido, usando un tubo de segmento y la tarjeta sanguínea

⚠ En el caso de que el paciente haya recibido una transfusión no programada desde la prescripción de GRASPA®, hasta la fecha programada de la administración de GRASPA, un nuevo test de compatibilidad debe ser realizado en su laboratorio local.

⚠ El producto no debería ser administrado en caso de discrepancias.

- Infunda toda la bolsa
- Purgar la línea de perfusión con suero fisiológico (de 20 a 40 ml de NaCl al 0,9%)

Etapa 3: DOCUMENTACIÓN

- Rellene la sección *«Administration of GRASPA®»* del documento Envío de GRASPA® y Administración «GRASPA® shipment and administration form».
- Envíe cuanto antes, después de la administración por fax el Documento «GRASPA® shipment and administration form» cumplimentado al +33 (0)4 78 78 93 05
- Conserve este Documento en la historia clínica del paciente

Etapa 4: DEVOLUCIÓN DE LA BOLSA (a ERYTECH Pharma)

- Tras la administración, coloque la bolsa vacía en el sobre previsto para ello (no incluya las líneas de perfusión)
- Consulte el procedimiento de devolución para realizar la recogida por el transportista

ORIGINAL

Fase 1: RICEVIMENTO DELLA SACCA

- Ricevimento della sacca sotto responsabilità medica
- Eseguire i controlli alla consegna descritti dalla voce *«Reception of GRASPA®»* del Documento «GRASPA® shipment and administration form»

Fase 2: SOMMINISTRAZIONE

- Attenersi alle regole di verifica finale (identità, esame del prodotto, controllo finale di compatibilità subito prima della somministrazione al paziente fra GRASPA® e il sangue del malato)

⚠ Nel caso in cui il paziente abbia ricevuto una trasfusione non programmata dalla prescrizione di GRASPA®, eseguire prima dell'iniezione un test di compatibilità presso il laboratorio di immunoematologia della vostra struttura (segmento disponibile sul prodotto).

⚠ In caso di anomalie, il prodotto non deve essere trasfuso.

- Somministrare per trasfusione tutto il contenuto della sacca
- Sciacquare i tubi con soluzione fisiologica (20-40 ml di NaCl al 0,9%)

Fase 3: TRACCIABILITÀ

- Compilare la sezione *«Administration of GRASPA®»* a tergo di questo documento.
- Inviare immediatamente per fax il Documento «GRASPA® shipment and administration form» completato (sezioni compilate) al +33 (0)4 78 78 93 05
- Conservare il Documento di trasporto e di iniezione di GRASPA® nella cartella clinica del paziente

Fase 4: RESTITUZIONE DELLA SACCA (a ERYTECH Pharma)

- Dopo la somministrazione, mettere la sacca vuota nel sacchetto previsto per tale scopo (non aggiungere i tubi)
- Richiamarsi alla procedura di restituzione per provvedere al ritiro da parte del trasportatore

GRASPA®
VALMISTEEN VASTAANOTTO JA ANTO

ORIGINAL

1. vaihe: PUSSIN VASTAANOTTO

- Pussin vastaanotto vastuullisesti lääketieteellisten käytäntöjen mukaan
- Suorita vastaanottotarkistukset « *Reception of GRASPA®* » ja injektioasiakirjan kohdan «GRASPA® shipment and administration form» mukaisesti

2. vaihe: ANTO

- Tarkista valmiste äärimmäisen tarkkojen tarkistussääntöjen mukaan (tunnistetiedot, valmisteen tutkiminen, GRASPA®-valmisteen ja sairaan henkilön veren yhteensopivuuden tarkistaminen viime kädessä potilaan vierellä).

⚠ Jos potilas on saanut GRASPA®-valmisteen määräämisen jälkeen verensiirron, jota ei ole etukäteen merkitty ohjelmaan, teetä ennen injektiota yhteensopivuustutkimus immuno-hematologisessa laboratoriossa (osio valmisteen päällä).

⚠ Jos havaitaan poikkeamia, valmistetta ei saa antaa potilaaseen.

- Anna pussin koko sisältö.
- Huuhtele letkut fysiologisella keittosuolaliuoksella (20 - 40 ml 0,9-prosenttista NaCl-liuosta).

3. vaihe: JÄLJITETTÄVYYS

- Täytä kappale « *Administration of GRASPA®* » joka on tämän asiakirjan toisella puolella.
- Lähetä «GRASPA® shipment and administration form» ja injektioasiakirja täydennettynä (osiot täytettyinä) viipymättä faksilla numeroon +33 (0)4 78 78 93 05
- Säilytä GRASPA®-valmisteen kuljetus- ja injektioasiakirja potilaan asiakirjojen joukossa

4. vaihe: PUSSIN PALAUTTAMINEN (ERYTECH Pharmalle)

- Kun valmiste on annettu, aseta tyhjä pussi sille varattuun kuljetuspussiin (älä laita letkuja mukaan).
- Pyydä kuljetusyritystä noutamaan lähetys palautusprosessia koskevien ohjeiden mukaisesti.

Appendix 7: Serious Adverse Event report form

PROTOCOL : GRASPA-AML 2012-01 EUDRACT NO : 2012-002026-78 IND NO : (For US only) IRB NO : (for US only)

Date of Report : |__|__| |__|__| |__|__|__|__| (*Day Month Year*) 25a. **Type of report** : ☐ Initial ☐ Additionnal n° |__|__|

Principal Investigator :	**Address :**

1. **Patient Initials:** |__|__| - |__| (*Last name First name*)	**Patient No:** |__|__|__|__| – |__|__| (*Site No Patient No*)	**Inclusion date:** |__|__| |__|__| |__|__|__|__| (*Day Month Year*)
1a. **Country**	2. **Date of birth:** |__|__| |__|__| |__|__|__|__| (*Day Month Year*)	3. **Gender:** ☐ F ☐ M	weight : |__|__|__| kg

I. EVENT INFORMATION

7. + 13. **EVENT** (primary diagnostic)**:** .....

4.-6. **Onset Date:** |__|__| |__|__| |__|__|__|__| (*Day Month Year*) **End Date :** |__|__| |__|__| |__|__|__|__| (*Day Month Year*)

Outcome:

☐ Recovering ☐ Not recovered ☐ Fatal ☐ Unknown

☐ Recovered (without sequelae) ☐ Recovered with sequelae, precise : .....

8.-12. **Seriousness** (tick appropriate boxes) :

☐ Death Date : |__|__| |__|__| |__|__|__|__|

☐ Hospitalization or prolonged hospitalization

Start date: |__|__| |__|__| |__|__|__|__|

Date of discharge : |__|__| |__|__| |__|__|__|__|

☐ Persistent/significant disability

☐ Life-threatening

☐ Result in congenital anomaly

☐ Serious according investigator judgment

Intensity :

☐ Mild (grade 1) : minor, no specific medical intervention

☐ Moderate (grade 2) : minimal or local intervention (non invasive)

☐ Severe (grade 3) : significant symptoms requiring hospitalization or invasive intervention

Or

Highly Severe (grade 4) : Life-Threatening, need for intensive care or emergent invasive procedure

Or

Death (grade 5)

7. + 13. **Description of tthe event** (manifestations, symptoms, laboratory results…):

Action taken regarding the event:

☐ None ☐ Corrective treatment, precise below :

Attached Documents: ☐ None

☐ Hospitalization report, nb of pages:…….. ☐ Exams report, nb of pages:…….. ☐ Laboratory results, nb of pages:……..

☐ Other, precise :.....

PROTOCOL : GRASPA-AML 2012-01 EUDRACT NO : 2012-002026-78 IND NO : (For US only) IRB NO : (for US only)

Patient initials : |__|__| - |__| *Last name First name* **Patient No :** |__|__|__|__| - |__|__| *Site No Patient No*

II. STUDY TREATMENT INFORMATION

14. **Treatment :** ☐ *GRASPA®* ☐ NA

15. Dose (per infusion)	16. Route	Number of infusions	18. 1st infusion date :	18. last infusion date :
……UI/kg.	……	|__|__|	|__|__| |__|__| |__|__|__|__| *Day Month Year*	|__|__| |__|__| |__|__|__|__| *Day Month Year*

Action taken regarding study treatment :
☐ None, Dose not changed (drug continued)
☐ Drug withdrawn (drug stopped)
☐ Dose reduced (or drug transitory discontinued)
☐ Not applicable

20. **Did event abate after stopping treatment**
☐ Yes ☐ No ☐ Not applicable

21. **Did event reappear after reintroduction :**
☐ Yes ☐ No ☐ Not applicable

Relationship to study treatment :
No Reasonable Possibility :
☐ Not applicable ☐ Not related ☐ Unlikely
Reasonable Possibility :
☐ Possible ☐ Probable ☐ Certain / Definite
☐ Not assessable

14. **Treatment** ☐ *CYTARABINE*

15. Dose (per administration)	16. Route	Number of administration	18. 1st administration date :	18. last administration date :
…….	……	|__|__|	|__|__| |__|__| |__|__|__|__| *Day Month Year*	|__|__| |__|__| |__|__|__|__| *Day Month Year*

Action taken regarding study treatment :
☐ None, Dose not changed (drug continued)
☐ Drug withdrawn (drug stopped)
☐ Dose reduced (or drug transitory discontinued)
☐ Not applicable

20. **Did event abate after stopping treatment**
☐ Yes ☐ No ☐ Not applicable

21. **Did event reappear after reintroduction :**
☐ Yes ☐ No ☐ Not applicable

Relationship to study treatment :
No Reasonable Possibility :
☐ Not applicable ☐ Not related ☐ Unlikely
Reasonable Possibility :
☐ Possible ☐ Probable ☐ Certain / Definite
☐ Not assessable

III. MEDICAL HISTORY AND ASSOCIATED MEDICATION

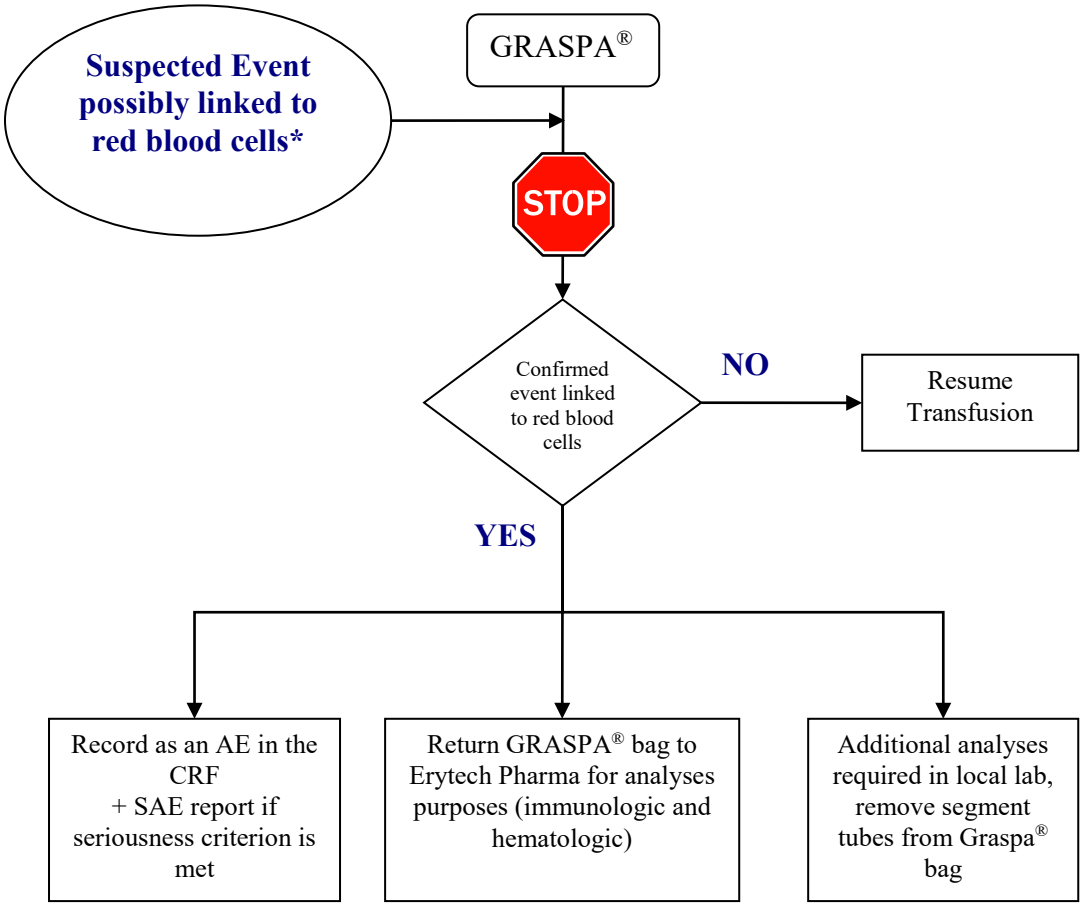
23. **Relevant medical history:** ☐ None

22. **Concomitants medication (except those for event treatment) :** ☐ None

Drug(s) (generic name)	Dose (daily)	Route	Indication	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	On going	Related to the event
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No
						☐	☐Yes ☐ No

Investigator completing the report (Name and address) :	**Signature**

Appendix 8: IMMEDIATE EVENT POSSIBLY LINKED TO RED BLOOD CELLS INJECTION



*

Chills / Fever	Shock
Hyperthermia	Dyspnea
Urticaria	Acute pulmonary oedema
Nausea, vomiting	Hypertension
Anxiety	Oligo anuria
Unexplained bleeding	Jaundice
Pains	Other suggestive clinical signs

Appendix 9: Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

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

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

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

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

Informed Consent

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

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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

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

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

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

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

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

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

Appendix 10: Patient Information Sheet - Informed Consent Form

PATIENT INFORMATION SHEET ON THE STUDY GRASPA-AML 2012-01

TITLE: A Phase IIb Trial Evaluating Efficacy and Tolerability of GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase) Plus Low-dose Cytarabine vs. Low-dose Cytarabine Alone, in Treatment of Newly Diagnosed Acute Myeloid Leukaemia (AML) Elderly Patients, Unfit for Intensive Chemotherapy. ENFORCE 1 study

Protocol Nº: GRASPA-AML 2012-01

Study sponsor: ERYTECH Pharma

INTRODUCTION

Your doctor has told you that you have Acute Myeblastic Leukaemia (AML). The purpose of this information sheet is to describe the disease and its treatments and to invite you to take part in some clinical trial.

The information given on this form is intended to help you to understand exactly what will be asked of you so that you can decide whether or not you want to take part in this study.

Please read this form and ask all the questions you want to ask before you decide whether or not to take part in the study. You can take as much time as you want before making your decision and you are free to discuss this with persons of your choice. Your participation in this study is completely voluntary and if you decide not to take part this decision will not disadvantage you in any way.

For this study, the Investigators and the hospital will receive financial funding to cover the research work

What is acute myeloblastic leukaemia (AML)?

The term leukaemia describes several types of cancer affecting the bone marrow where blood cells are produced. Leukaemia occurs when blood cells that are still immature (precursors) become cancerous or can no longer mature or specialise normally. These cells are called “blasts” or “blastic cells”.

In contrast to chronic forms of leukaemia, which progress very slowly, acute forms of leukaemia can occur from one day to the next and progress rapidly. They are characterised by abnormal multiplication of precursors. Uncontrolled multiplication of abnormal blasts leads to invasion of the bone marrow which can no longer function properly. In particular it can no longer produce normal blood cells. This is known as medullary insufficiency.

In the acute forms of leukaemia, a distinction is made between acute lymphoblastic leukaemia (ALL), which affects the lymphocyte line (a category of white cells involved in the immune system) and forms of acute myeloblastic leukaemia (AML), which may affect the precursors of all the other cells produced by the bone marrow (the red cells that transport oxygen to the tissues, the white cells that fight infection and the platelets that play a role in blood clotting).

The latter form of leukaemia can lead to anaemia (reduction in red cells and haemoglobin) which causes fatigue, paleness, shortness of breath and palpitations. Because of the drop in other white cells called polymorphonuclear neutrophils (neutropenia), the body is more sensitive to infections, particularly pulmonary infections. Finally, the lower number of platelets (thrombopenia) may cause bleeding, particularly of the mucosa (nosebleeds, bleeding gums) and skin (haematoma or bruises as a result of minor bumps). The accumulation of blasts in the bone marrow and in other organs may cause other problems: bone pain, enlargement of the lymph nodes, spleen and liver.

What is the treatment for AML?

The treatment for this disease varies according to the patient’s age. While patients aged less than 60 years can benefit from “intensive” chemotherapy combining several anticancer medicines, older patients are

less robust and far less able to tolerate the adverse effects caused by this kind of treatment which is then as dangerous as the disease itself. Treatment for these patients, described as “non-eligible" for intensive chemotherapy, is based on a single low-dose chemotherapy product, which is used to limit the harmful side effects while eliminating as many of the cancer cells as possible.

You are in this category of patients and your doctor has offered you a treatment based on low-dose cytarabine, given in 10-day courses repeated every month (about 28 days). If side effects occur on this treatment, your doctor will offer you appropriate medicines for the situation and may have to change the cytarabine dose or discontinue this medicine.

Why is this study being conducted? What is the benefit for the patients?

Patients over 60 years old cannot always be given intensive chemotherapy. It is necessary to evaluate every possible alternative treatment to be able, in the absence of the ability to cure the disease completely, to slow disease progression, bring relief to patients and prolong their life expectancy under good conditions.

In this study, we propose to evaluate the addition of the product GRASPA, containing L-asparaginase, to “conventional” treatment with low-dose cytarabine. Approximately 120 patients will participate in this study which will take place in France and other European countries.

L-asparaginase decreases the quantity of asparagine, an amino acid necessary for the leukaemia cells to survive. There is a higher chance of eliminating the cancer cells by depriving them of asparagine with L-asparaginase. This compound is a basic treatment used for 40 years in acute lymphoblastic leukaemia. Certain research studies suggest that L-asparaginase could be equally active in acute myeloblastic leukaemia. L-asparaginase is currently used in treatment protocols for this disease in children.

ERYTECH Pharma has developed a form of L-asparaginase that is encapsulated in red blood cells. This product is called GRASPA. It is not yet on the market. It resembles a bag of blood and is given in the same way as a blood transfusion. Studies have already been conducted in animals and humans with this product. They show that GRASPA is less rapidly eliminated than L-asparaginase and thus has a longer action in the body and is better tolerated by patients. Allergic reactions are decreased in particular. All the same, administration of GRASPA may cause adverse effects and your doctor may have to stop using it if you experience the effects listed below for L-asparaginase.

As the studies on GRASPA are still on going, expected efficacy is not fully known and you may have no benefit to be treated with this product.

Undesirable effects with GRASPA®

Adverse events that may occur with GRASPA® are those related to transfusion and those related to L-asparaginase.

Major clinical signs of adverse reaction due to transfusion are feeling of heat, feeling of burning along the vein, chills, fever, abrupt change in blood pressure, malaise, nausea with or without vomiting, difficulty to breath, urticaria, rash, localized or extensive oedema, anaphylactic shock

Most frequent and potentially severe adverse reactions related to L-asparaginase toxicity are the following: Immediate-type hypersensitivity reactions, troubles in liver and pancreas function, troubles in coagulation, thrombosis, diabetes mellitus, and general disorders such as fever, pains (abdominal, back, and joint pain) and gastrointestinal disturbance.

Even if the participants in this study are aged 65 years and above, it is important to remember that pregnant women or women breastfeeding a baby cannot take part in this study in view of the toxic effects of the anticancer medicines administered in the courses of treatment and transmission of these effects to the baby.

Women of childbearing potential and males must agree to use adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for the duration of study treatment and for 6 months after the last dose of cytarabine or 4 months after the last dose of Graspa (whichever is the longest)

What is the purpose of this study?

The purpose of this study is to evaluate the efficacy and tolerability of GRASPA administered in combination with low-dose cytarabine compared to cytarabine alone.

Efficacy (response to treatment) is mainly evaluated by measuring the overall survival for a period of 24 months. Tolerability is mainly assessed by studying the nature and frequency of the adverse events.

The study has also an exploratory part which is optional, consisting in performing an analysis of potentially relevant biomarkers, utilizing proteomic and transcriptomic techniques on bone marrow biopsy/aspirate. Also cells isolated from the bone marrow samples will be cultured and tested for sensitivity to asparaginase. The aim of this part is to better understand mechanisms of action, improve treatments or develop new medicines. You will be asked to sign a separate Informed Consent Document, if you agree to participate in this exploratory study also.

What will the study involve?

If you agree to take part, your doctor will carry out some investigations to check the selection criteria for patients in the study (in particular a screening test for hepatitis B and C and AIDS) and then you will start the study treatment that you are given (you do not have to pay for it). This study compares treatment arms A and B described below. Which one you are allocated is decided at random with 2 chances in 3 of having treatment B (with GRASPA):

- Treatment arm A: subcutaneous administration of low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily) for 10 consecutive days (Day 1to day 10, D1 to D10), which makes up a course. The courses are repeated every month (about 28 days +/- 3 days). This is equivalent to normal management for treatment of a disease like yours in patients aged over 60 years.

-Treatment arm B: Administration of Cytarabine similarly as for treatment arm A with addition of GRASPA, administered at a dose of 100IU/kg as in intravenous infusion, immediately after cytarabine treatment (D11).. The courses are repeated every month (about 28 days +/- 3 days).

The study treatment will be reduced/stopped if you cannot tolerate it or if your doctor thinks that another treatment would be more suitable for your condition, depending on your state of health, the progression of your disease or the side effects that occur or if you do not want to continue with the treatment.

What will you be asked to do?

Your total participation in the study will be 24 months maximum from the day when you start the study treatment (but your doctor will continue to monitor your disease beyond this period, after the end of the study). Similarly, the treatment, if still beneficial and well tolerated, can be given to you beyond this period. You will be asked to attend the consultations with your doctor for follow-up of the disease and the repeat administrations of treatment. You should also undergo investigations such as blood samples and bone marrow punctures.

The follow-up visits will take place once a month while you are receiving the study treatment. Your doctor will perform a clinical examination and monitor your tolerance of the treatment and its efficacy (blood samples and bone marrow analyses). After you stop the study treatment, the follow-up visits will take place every 3 months up to the 24 months' duration of the study period.

During the inclusion visit, the following procedures/assessments will be performed:

- Assessment of general health status (performance status)
- You will be asked about your medical history and details of AML status will be collected (including collection of characteristics of AML, ex. results of cytogenetic analysis etc.) as well as other medication you could take concomitantly
- A general physical examination by systems and organs, weight and height measurements will be performed
- Blood samples will be collected for laboratory tests: hematology, biochemistry, serology test (including HIV, hepatitis B and C, if needed)

Subsequent visits: monthly visits during treatment period and End of treatment visit:

- Disease evaluation (AML)

- Clinical assessment: vital signs (height, weight, pulse, blood pressure systolic and diastolic), performance status, physical examination
- You will be asked to complete a questionnaire about your quality of life called EORTC QLQ-C30,
- Blood samples will be collected for laboratory tests: hematology, biochemistry at D1, D5, D9, D13, D18, D23 and D27
- You will be asked if you had any adverse events since the last visit and if there was any change in concomitant medications you may take. Please pay attention: before administration of any new drug, please ask your study doctor about as there could be drugs which interfere with study medication.
- You will receive at each visit a patient diary to be completed with the dates of cytarabine administration and with all adverse events that you felt – you must return this diary at each visit and your doctor can ask you details about these

Follow-up visit after end of study treatment: every 3 months +/- 2 weeks after End of Treatment visit – ex. M3, M6, M12…)

- Disease evaluation (AML) if needed,
- You will be asked to complete a questionnaire about your quality of life called EORTC QLQ-C30-
- You will be asked if you had any adverse events since the last visit and if there was any change in concomitant medications you may take.
- Additionally, at minimum, your doctor will call you 4 months (+/- 1 week) after end of treatment, to ask you about any new adverse events

For patients given treatment B: in addition to the blood samples described above, your doctor will take specific additional blood samples. These samples will be used to measure the total quantity of L-asparaginase remaining in your blood, its activity, the level of asparagine depletion, as well the levels of aspartate, glutamine and glutamate (these are blood components, whose levels are modified by GRASPA) (analysis known as pharmaco-kinetics and pharmaco-dynamics tests, PK/PD) and the potential existence of antibodies to asparaginase (known as immunogenicity analysis).
These additional PK/PD tests will be performed only for the next two courses after the acceptance of this consent and will be performed as follows:

- D9: a sampling for PK/PD analysis
- D11 : a sampling for immunogenicity analysis and samplings for PK/PD analysis at : 15 minutes +/- 10 min before GRASPA administration, then after administration at 5 min +/- 2 min, 1 h +/- 10 min, 3h +/- 10 min, 6 h +/- 10 min
- D18 - 7 days later, after administration, a sampling for PK/PD analysis
- D27 – at course end, 16 days after GRASPA administration, a sampling for PK/PD analysis

These additional tests will be performed in the following laboratories:

- Total L-asparaginase and aminoacids :

SGS Cephac Europe
90 Avenue des Hauts de la Chaume, B.P. 28,
86281 Saint Benoît Cedex, France

- Anti-asparaginase antibodies : Hôpital Hôtel Dieu – Nantes, France – will be tested during all treatment

The total additional quantity of blood taken will be about 6 ml per PK/PD sampling and 2 ml for immunogenicity sampling. Certain blood samples collected may be stored for a single final assay (L-asparaginase, asparagine, aspartate, glutamine and glutamate and antibodies above mentioned) at the end of the study. Samples will be kept frozen in analysis laboratory until the end of the study and will be then destructed, under sponsor responsibility. No further analysis will be carried out without the patient is informed, however some samples may be used for calibration of measuring equipment, without analysis. No collection of blood samples is expected beyond this period.

The biological samples collected during the study will be treated in accordance with the Law 14/2007 on Biomedical Research.
If you do not receive the treatment with GRASPA, these additional blood samples will not be requested.

Your doctor will assess the effect of the study treatment and disease status every month by taking a blood sample combined or not with other routine tests used for assessing the status of your disease. Samples of bone marrow (called a biopsy or bone marrow puncture) will also be taken every 2 months.

This procedure may be painful, but only for a few seconds. You may feel a sharp sting and burn when the anesthetic numbs your skin over the aspiration or biopsy site. You may hear a crunching sound and feel pressure and some pain when the needle enters the bone. During an aspiration, you may feel a quick, shooting pain down your leg as the sample is taken.

The biopsy site may feel stiff or sore for several days after the biopsy. You may have a bruise on the site.

Serious problems from a bone marrow aspiration or biopsy are not common. Problems may include:

- Bleeding from the biopsy site (People with bleeding problems have a higher chance for this),
- Infection of skin or the bone (osteomyelitis) at the biopsy site,
- Injury to your heart, a lung, or a major blood vessel if the sample is taken from the breastbone (sternum). This complication is very rare. Samples are not often taken from the breastbone, so most people do not have to worry about this risk.

If you agree, a part of the bone marrow samples, taken before and after the treatment begins, will be sent to ERYTECH Pharma for the purposes of exploratory research, as explained previously.

Legal issues

Your doctor has told you about the disease and its normal treatment. He has invited you to take part in this study, GRASPA-AML 2012-01, the sponsor of which is ERYTECH Pharma.

Your participation in this study is entirely voluntary.

If you do not want to take part in this research, you will continue to benefit from suitable medical management of your disease.

If you agreed to take part in this study, we shall ask you to sign the consent form on the last page. Your signing this, before you are involved in the study, does not affect your legal rights in any way. If you wish, you can ask your doctor to tell you about the overall results of the study. In addition, your doctor will let you have any new information about the study or study treatment for the whole time the study is being conducted.

This study will be conducted in accordance with national legislation relating to the rights of patients involved in biomedical research (Protection of personal data will be complied with laid out in Organic Law 15/1999, enacted on 13 December and the Royal decree 1720/2007)

Your doctor and / or the institution will receive financial compensation for their participation

This study protocol has been also approved by the Ethics Committee and regulatory authorities.

According to the LOPD 15/1999, you have the right to cancel the data or to ask to be shown what data about you has been collected and if you think anything is incorrect you may ask to have it corrected.

Erytech Pharma S.A., the sponsor of this biomedical research, whose head office is situated at Bâtiment Adénine, 60 Avenue Rockefeller, 69008 Lyon, has taken out insurance in accordance with the legal provisions which covers its civil liability and that of anybody involved, with HDI Gerling, Industrie Versicherungs-AG, Riethorst 2 – D 30659 Hannover, (policy no.XXXXXX).

Right to refuse to take part or to leave the study

You are free to agree or to refuse to take part in this research. If you do not wish to take part in this study you will receive appropriate treatment for your disease without administration of GRASPA.

If you decide to take part, you are still free to stop the research at any time without having to give reasons and without incurring any disadvantages in relation to the care you will be given. Your decisions will not affect the care you will receive.

The doctor who monitors you during this study may decide at any time to discontinue your participation in the research if he considers that the research may harm you, if you do not follow the instructions that your monitoring while on treatment requires or if the study as a whole has to be stopped.

Confidentiality

As part of the biomedical research that ERYTECH Pharma has invited you to take part in, your personal data will undergo data processing so that the research results can be analysed with regard to the aim of the research. Your consent to participate in this study also includes your consent to use your medical and clinical data for research purposes.

The sponsor, ERYTECH Pharma is responsible of the recording of collected data

To this end, your medical data will be sent to the Sponsor of the research or to the persons or companies acting on his behalf and, if necessary, to health authorities (in France or abroad) comply with that laid out in Organic Law 15/1999, enacted on 13 December and the Royal decree 1720/2007. These data will be identified by a code number to guarantee your anonymity.

Your participation in the study remains strictly confidential. All the information you give your doctor, as well as the medical data, will also be confidential. However, in this connection, the persons appointed by the authorised institutions and the authorised members or their representatives can check your personal data to ensure that this study has been conducted in accordance with the applicable legislation and health authority regulations.

The information from the data in your file will be used for this study only and for the publications that may be based on the results obtained. Your identity will be protected in any case. The medical data about you cannot be used for purposes other than those of this research or be communicated to third parties without your permission.

In accordance with the provisions of the Law, you have the right to access your personal data and an opportunity to correct them. You also have the right to object to transmission of the data covered by professional confidentiality that may be used as part of this research and may undergo data processing.

Ask the doctor who has invited you to take part in this study if you think that the explanations you have been given are inadequate and you want more detailed information.

WRITTEN INFORMED CONSENT FORM FOR PARTICIPATION IN GRASPA-AML 2012-01 STUDY

After discussing and obtaining answers to all my questions, I the undersigned

(patient's surname and first name),

……..

AGREE FREELY AND VOLUNTARILY TO TAKE PART IN THE BIOMEDICAL RESEARCH ENTITLED: A Phase IIb Trial Evaluating Efficacy and Tolerability of GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase) Plus Low-dose Cytarabine vs. Low-dose Cytarabine Alone, in Treatment of Newly Diagnosed Acute Myeloid Leukaemia (AML) Elderly Patients, Unfit for Intensive Chemotherapy, ENFORCE 1 study, sponsored by ERYTECH Pharma which I was invited to take part in by **Professor / Dr. (doctor's surname and first name)**

.....

Telephone number to reach your physician, including for emergency needs: **TEL :……..**

the investigator in this study from whom I can request any additional information at any time.

On the understanding that:

- The doctor who invited me to take part in this research on the conditions described in the information letter has given me all the information I wanted about the nature, aim, duration and foreseeable effects of the study and I have been informed of what is expected of me.
- The potential benefits and risks of the study have been explained to me and I have been able to ask all the questions I wanted during the discussion with the doctor. All my questions have been answered to my satisfaction and I can ask for additional information at any time.
- I understand that I am free to choose whether or not to take part in this research and I can decide to end my participation at any time, for any reasons whatsoever and without bearing any liability; however, in this case I undertake to inform my doctor as soon as possible. The fact that I am taking part in this research will not affect my relationship with my doctor who will offer me, if I want and if necessary, another appropriate treatment.
- My consent does not release the investigator and sponsor from all their responsibilities and I retain all my rights guaranteed by in compliance with as stipulated in Royal Decree 223/2004, which regulates clinical trials. . I have also been informed of the existence of insurance covering the procedures associated with the study and that this study has been submitted for approval to the Ethics Committee and health authority
- The data about me collected during this research, including this consent form or laboratory results, will remain strictly confidential but can be subject to data processing conducted by the organisers of this research comply with that laid out in Organic Law 15/1999, enacted on 13 December and the Royal decree 1720/2007. However, the persons involved with this study will be entitled to consult them.
- I agree that the results of this study may be communicated to the authorities concerned, the study sponsor and the scientific community (within or outside France/Europe). I know and I agree that the sponsor or its representatives and the authorities can inspect my medical data to check the information collected.

- My participation on this research means that I will not be able to participate in another biomedical research for the duration of this research.

Two copies: one for the patient and one for the doctor

Person agreeing to participate: Surname ..... First name ..... Patient's signature ..... Date |__|__| |__|__| |__|__|__|__| (patient must personally write his/her name, sign and date)
I hereby confirm that I have fully informed the patient named in the above of the nature, purpose, practical details as well as the risks associated with the study. The patient has read the information form and has kept a copy of it. He/she has given his/her voluntary agreement to participate in the biomedical research study GRASPA AML 2012-01. Surname ..... First name ..... Investigator's signature ..... Date |__|__| |__|__| |__|__|__|__|

INFORMATION LETTER FOR USE OF THE BONE MARROW SAMPLE

Dear Sir or Madam,

Your doctor is going to take a bone marrow sample. This sample will be used to establish the diagnosis of your disease and to tailor its treatment.

We are writing to ask for your permission to use a part of this bone marrow sample for the purposes of scientific research which could help to understand mechanisms of action, improve treatments or develop new medicines. You are free to agree or to refuse your permission for use of your sample in this purpose. You can also change your mind at any time without giving reasons; in this case, no further analysis will be performed and without penalty or loss of benefits to which you are otherwise entitled, however, the results of the analysis already done can be used for scientific purposes.

This research consists in performing genetic tests (tests on cells which look for changes in DNA or RNA) and biomarker tests (tests that look for substances such as proteins that tell the drug is working in your body) utilizing specific techniques. The researchers will study how changes in the cells' information and biomarker levels might affect the disease's response to study treatment, the course of the disease and your response to treatment.

Also cells isolated from the bone marrow sample will be cultured and tested for sensitivity to asparaginase (one of a drug we are testing used to treat acute myeloid leukemia).

Your sample will be anonymized and your name will not be recorded.

The samples will be sent to ERYTECH Pharma, a pharmaceutical company in Lyon, where part of analysis will be done as well as to the MD Anderson Cancer Center (Houston, Texas, USA) and/or another central laboratory (within Europe or United States of America- USA-) who performs specific method of analysis under ERYTECH responsibility. The analyses conducted by ERYTECH Pharma on your sample are part of a clinical trial with reference GRASPA-AML 2012-01. If you meet all the selection criteria for patients, your doctor may invite you to take part in this clinical trial. He will then explain the aims of the study to you, give you the information documents and ask you for your consent to take part. If you agree, further bone marrow samples will be taken for evaluation of the disease and part of these samples will be sent to Erytech Pharma for use in the same conditions and purpose as described above.

DECLARATION OF CONSENT

I the undersigned

Full Name: ……

Date of birth: ……

Declare that I have understood the information given above and agree for the use of a part of the bone marrow sample for the purpose of scientific research and I understand and agree that this (these) sample(s) will be sent to ERYTECH Pharma and to other laboratory(ies) (within Europe or USA).

Signature of the patient:

.....

Date .....

(patient must personally write his/her name, sign and date)

I hereby confirm that I have fully informed the patient named in the above of the nature, purpose and practical details of this research. The patient has read the information form and has kept a copy of it. He/she has given his/her voluntary agreement to participate.

Investigator's name:
……

Investigator's signature
..... ***Date*** |__|__|__|__|__|__|__|__|

Appendix 11: History of changes

Version, date	Main changes
Version 1, 03 Aug 2012	initial version
Version 2, 30 Nov 2012	protocol changes requested by France Regulatory Authority, mainly: - Establish a minimum treatment cycles number: defined to 1 - Limit the age of patients at inclusion to ≤ 85 years - Precise the "unfit for intensive chemotherapy" to non-eligible to receive intensive chemotherapy: added "at risk to suffer treatment related pejorative toxicities /early death" - Clarification of Inclusion criteria "Evidence of post-menopausal status for female patients" : added "absence of menstruation for 12 months" - Precise the contraindications of Aracytine in exclusion criteria as per France SPC of Aracytine: added in the protocol - Clarification of exclusion criteria: o History of grade 3-4 pancreatitis or grade 3-4 thromboembolic event (according NCI-CTCAE Version4.0) o Patient presenting evolutive cancer other than AML, except in situ basal-cell carcinoma or in situ cervix cancer - Note on primary endpoint: changed from EFS to PFS - Note that the protocol should include only patients with life expectancy of ≥ 3 months: added in the protocol in inclusion criteria - Change the SCP of CYTOSAR to SPC of Aracytine 100mg in appendix 1
Version 3, 05 Dec 2012	added protocol changes requested by France Regulatory Authority: o Request addition of HIV, hepatitis B and C testing at screening o Added creatinine clearance as lab test o Updated Appendix 8 of drugs causing hemolysis
Version 4, 21 Jan 2013	- Location: France changed to Europe - Clarification of secondary endpoint "hospitalization": except schedule protocol visit - Clarification of secondary endpoint on PK/PD – instead of Free and encapsulated L-asparaginase activity, Total L-asparaginase activity will be measured; consequently, the section on Plasma L-Asp measurement was deleted and the one on total L-Asp changed accordingly. - Correction of immunogenicity timepoints needed: only at Day (D)11, and not at D11 and D18. - Added "Disease (AML) progression, as well as death as consequence of disease evolution" as an exception to AE reporting.
Version 5, 20 Nov 2013	- Clarification of patient age for inclusion: "Patient over (or equal to) 65 years old and less than (or equal to) 85 years old" - Clarification to exclude this particular patients that have poorer prognostic: o "Patient with Secondary AML consecutive to anterior malignant hemopathy as:

	▪ Myelodysplastic syndrome diagnosed more than 6 months before study entry ▪ Myeloproliferative syndrome” - Revision of the restriction regarding cardiac insufficiency from LVEF < 50% of the theoretical value to ≤40 %, considering that the study treatment tested have no cardiotoxic effect and also the age of population targeted - Clarification of randomization and stratification procedure - Clarification on dose adaptation to confirm that patients discontinuing GRASPA or LDC (for an AE) are maintained in the study: “Dosage adaptation: •Low-dose cytarabine (LDC) The dosage could be adjusted to 20 mg daily in case of toxicities at investigator's decision. Investigator may also consider temporary or definitive withdrawn of LDC if necessary. In such case, for patients in arm B, GRASPA should be continued as scheduled, every 28 days. •GRASPA If patient cannot receive GRASPA for other reason than toxicity, GRASPA should be postponed no later than one week after the initial schedule day, and, in any case should be resumed at the next block. If GRASPA cannot be resumed and must be definitively withdrawn for any reason, patient should be kept under LDC.” - Clarification on attention to be paid to diabetic patients treated with oral hypoglycemic agents and not only with sulfamides. - Modified collection of patient initials: to be restricted as per local regulations - Updated SAE form, as per internal review.
Version 6, 05 May 2014	- Clarification of study title to align with inclusion criteria: “elderly patients” instead of “over 65 years” - Clarification of inclusion criteria “Subscription to social security insurance”: added “(if applicable in accordance with local regulations)” as this is required by French authorities, but not necessarily by other countries. - Addition/clarification of following exclusion criteria as per BfArM request: o “Total bilirubin > 2 ULN o INR > 1.5 o Insulin-dependent or uncontrolled diabetes mellitus o Active cancer other than AML, except in situ basal-cell carcinoma or in situ cervix cancer o Severe active infection, HIV seropositivity, or active type B or C viral hepatitis” o Sexually active man of potential fertile couple not willing to use highly effective contraceptive method - Added section “8.5 Dosage modification in case of toxicity” as per BfArM request - Clarification of concomitant treatment requests - Modifications of section “Adverse Events Reporting” as per BfArM request, mainly:

	○ Collection of all clinically significant AEs ○ SAE reporting within max 24h - Clarification of DSMB review timepoints
Version 7, 05 Oct 2015	- Change of primary endpoint from Progression free survival (PFS) to Overall survival (OS) - Change of PK/PD sampling to allow for more samplings after GRASPA infusion - Added “eryaspase” as proposed INN, instead of “L-asparaginase encapsulated in erythrocytes” - Re-definition of response criteria in AML and clarification of assessment requirements - Clarification of some inclusion/exclusion criteria, mainly: - Unfit for intensive chemotherapy - Contraception period - Accepted lab tests upper values - Updated contraindications, concomitant medication and precautions for use sections to be in line with the proposed GRASPA SPC - Updated/clarification of study flow chart - Updated statistical plan section as well as other relevant sections according to changes above