Phase II study with Ga101-DHAP as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients before High-Dose chemotherapy BEAM with autologous stem cell transplantation (ASCT).

STUDY DRUG Obinutuzumab (GA101)

Study ID Phase II GA101-DHAP

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I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

_____

Investigator's Signature Date

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Name of Investigator (Typed or Printed)

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1 BACKGROUND AND INTRODUCTION

1.1 Diffuse large B cell Lymphoma

Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma subtype, accounting for roughly 30-40% of all non Hodgkin Lymphoma (NHL) in adults, and its incidence is increasing. Median age at diagnosis is 55-60 years.[1,2]

The addition of rituximab to first line anthracycline-containing chemotherapy has significantly improved the prognosis of DLBCL patients at any stage and age, and data of original trials have been recently been confirmed after longer follow up.[3,4,5] Furthermore, dose-dense and dose –intense chemoimmunotherapy is supposed to have added further improvement in DLBCL outcome and results of ongoing prospective trials are soon expected.[6]

1.2 Relapsed /refractory DLBCL

Despite the improvement with first line treatment in the rituximab era, a proportion of DLBCL patients still relapse and need further treatment.

In younger patients, induction chemotherapy followed by high dose consolidation and autologous stem cell support (ASCT) represents the gold standard since the publication of the PARMA trial.[7] Approximately 50% of all relapsed patients can be cured by this strategy, with main prognostic factors being represented by duration of first response,[8-9] International Prognostic Index at relapse (secondary IPI, sIPI),[10-11] and chemosensitivity to salvage therapy before ASCT.

More recently, the achievement of complete remission (CR) defined by PET negativity as per Cheson 2007 criteria[12] has emerged as a strong discriminant at transplantation.[13-15] Thus, further efforts to increase PET negative rate at transplantation are highly needed.

The addition of rituximab to second line chemotherapy significantly improves the outcome of patients non-pretreated with rituximab during first line treatment.[16] Otherwise, recent retrospective[17] as well as a randomized prospective (CORAL)[18] trials have pointed out the lower likelihood of obtaining an objective response with second-line chemotherapy in patients failing first line rituximab-containing regimens. The CORAL[18] trial randomly compared R-DHAP and R-ICE as induction regimens before ASCT: overall response rate (ORR) was 83% in patients without as compared to 51% in those with prior exposure to rituximab, and CR rate was as low as 30% in cases previously treated with rituximab. Both 3-year event-free survival (EFS, 47 vs 21%) and overall survival (OS, 66% vs 40%) were

also significantly affected by previous treatment with rituximab. As virtually all patients with relapsed DLBCL are actually pretreated with rituximab, strategies to improve ORR through the addition of other active compound to R-chemotherapy in the induction phase are warranted.

1.3 Obinutuzumab (GA101)

RO5072759 (GA 101) is the first Fc-engineered type II CD20 humanized IgG1 antibody [19 20]. The type II antibodies exhibit lower C1q binding and CDC compared with type I. In this type II antibodies is increased the direct and immune effector cell-mediated induction of B-cell death. An additional factor that contributes to the increased ADCC induction by GA 101 is the higher binding affinity of the antibody to FcyRIIIa receptor achieved via Fc glycoengineering. In vitro studies showed that if compared with Rituximab, GA 101 exhibited 10- to 25-fold greater potency and was 1.5- to 2.5-fold more effective in terms of absolute B-cell depletion. In addition, GA 101 demonstrated in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Of particular interest are the results in second line therapy setting using human SUDHL-4 DLBCL model subcutaneously injected in mice. All animals were pre-treated with rituximab at the dose of 30 mg/Kg, when the tumors regrowth animals were randomized to three treatment: rituximab (30 mg/Kg), GA 101 (30 mg/Kg) or vehicle. Tumors continued to grow rapidly in rituximab and vehicle treated group whereas the treatment with GA 101 was able to control tumor growth [21].

Characteristics of this humanized glycol-engineered antibody:

- High-affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity (CDC) activity related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody-dependent cellular cytotoxicity (ADCC) related to an improved binding of GA101 to the different allotypes of FcγRIIIa expressed by natural killer cells and monocytes
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino acid exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell-death induction, it is possible that GA101 may have greater efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism.

1.3.1 Pre-clinical efficacy with GA101

GA101 has demonstrated in vivo efficacy superior to that of rituximab in various human lymphoma xenograft models. Both antibodies have been compared in human SUDHL-4 cells (a DLBCL model) that were subcutaneously injected into severely immunodeficient beige mice. Therapy began when tumors were established and were rapidly growing. It was shown that, at 10 mg/kg, rituximab inhibited tumor growth more than rituximab at 1 mg/kg; however, increasing the dose to 30 mg/kg did not result in increased efficacy of rituximab.In contrast, GA101 showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg and resulted in complete tumor regression in all animals and in lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have also shown similar results, in which GA101 treatment was able to control tumor growth when vehicle- and rituximab-treated tumors were not controlled [22].

1.3.2 Clinical experience with GA101

For more detailed clinical information on GA101, please refer to the current version of the Investigator's Brochure.

As of June 2013, clinical data on GA101 regarding efficacy and safety are available from four Phase I/II studies (BO20999, BO21003, BO21000, and JO21900) and two Phase III studies (GAO4753g and BO21004/CLL-11). As of 2 July 2013, an estimated 503 CLL patients and 1476 NHL patients from the 12 studies have been exposed to obinutuzumab, either as monotherapy or in combination therapy.

Phase II results from the aggressive and indolent NHL cohorts of patients in ongoing studies are described below. For information about chronic lymphocytic leukemia (CLL) and all Phase I studies, please refer to the GA101 Investigator's Brochure.

Study BO20999 (Phase I/II): GA101 Monotherapy

The results from the Phase II part of the study are presented as follows.

Patients with Indolent NHL. Forty patients with relapsed or refractory indolent NHL were randomized to receive GA101 in a low-dose (LD) cohort (n = 18) or a high-dose (HD) cohort (n = 22). Patients were pre-treated with a median of four prior regimens (range: 1–13), and the majority (39 of 40 patients) had received prior rituximab treatment. More than half of these patients (24 of 40) were considered to be rituximab refractory, and 25% (10 of 40) of all patients had previously received an autologous stem-cell transplant. The treatment regimen in the LD cohort was 400 mg for Cycles 1–8 (21-day cycles), with an additional 400-mg dose on Day 8 of Cycle 1. The treatment regimen in the HD cohort was 1600 mg on Days 1 and 8 of Cycle 1 and 800 mg for Cycles 2–8 (21-day cycles). The end-of-treatment response rate (response evaluation 4 weeks after the end of treatment) was 17% in the LD cohort (3 patients with partial response [PR], 6 with stable disease [SD], 7 with progressive disease [PD], and 2 unevaluable) and 55% in the HD cohort (2 patients with CR, 10 with PR, 6 with SD, and 4 with PD).

GA101 was well tolerated in both cohorts. During the treatment period, 9 patients experienced a total of 12 serious adverse events, with four events (herpes zoster, neutropenia, febrile neutropenia, and pancreatitis; all in the HD cohort) assessed by the investigator as related to GA101. During the additional follow-up period, 2 patients experienced serious adverse events of pyrexia (LD cohort) and bacteremia (HD cohort). The most common adverse events (all grades), occurring with an incidence of ≥ 10%, were infusion-related reaction (IRR; 73%), asthenia (33%), nasopharyngitis (13%), peripheral edema (10%), pyrexia (10%), abdominal pain (10%), bronchitis (10%), and nausea (10%). Thirty-three percent of patients had Grade 3 or 4 adverse events, the three most common being lymphopenia (8%), neutropenia (8%), and infections (10%).

Patients with Aggressive NHL. Forty patients with aggressive NHL were enrolled in the Phase II part of the study. Of these patients with aggressive NHL (25 with DLBCL and 15 with mantle-cell lymphoma [MCL]), 19 were treated in the HD cohort (15 with DLBCL and 4 with MCL) and 21 in the LD cohort (10 with DLBCL and 11 with MCL). Preliminary safety and efficacy data are available (data on file). The primary endpoint was end-of-treatment response, assessed 4 weeks after the last infusion (25 weeks after treatment start). Patients were heavily pre-treated (median of three prior therapies), with 63% of patients having not responded to or relapsed within 6 months after a previous rituximab-containing regimen (rituximab refractory), and 45% of patients completed all nine infusions. The end-of-treatment response rate was 24% (DLBCL: 2 patients with PR, 1 with CR unconfirmed;

MCL: 2 with CR) in the LD cohort and 32% (DLBCL: 4 with PR; MCL: 2 with PR) in the HD cohort.

The five most common adverse events were IRR (75%), infection (25%), asthenia (18%), anemia (15%), and lymphopenia (15%). Fifty percent of patients had Grade 3 or 4 adverse events, with the five most common being lymphopenia (15%), anemia (10%), thrombocytopenia (8%), IRR (8%), and tumor lysis syndrome (5%). Serious adverse events occurring in 2 or more patients included cardiac failure ($n = 2$), IRR ($n = 3$), tumor lysis syndrome ($n = 2$), and anemia ($n = 2$). There was one Grade 5 adverse event, cardiorespiratory arrest, which was thought to be secondary to ventricular arrhythmia.

Study BO21003 (Phase II): GA101 Monotherapy plus Maintenance

This is an ongoing, open-label, multicenter, randomized, Phase I/II study to investigate the efficacy and safety of GA101 monotherapy compared with rituximab monotherapy in patients with relapsed indolent NHL. The Phase II portion of the study began in July 2009, and approximately 176 patients have been enrolled. An interim analysis for safety and a futility analysis for efficacy was performed in July 2010 using data from 78 patients. According to the protocol, futility stopping rules recommended a halt to the trial if the rituximab arm had 2 or more patients with a response at the end of treatment than the GA101 arm ($\Delta < -3.14\%$). The internal monitoring committee's recommendation was to continue the study as planned. No new safety issues were identified.

Study BO21000 (Phase Ib): GA101 in Combination with Chemotherapy

Study BO21000 is an ongoing trial, investigating two doses of GA101 (400 mg and 1600/800 mg) in combination with chemotherapy given every 4 weeks for a maximum of six cycles (GA101 plus fludarabine and cyclophosphamide [G-FC]), or a maximum of eight cycles (GA101 plus CHOP [G-CHOP]) in patients with relapsed follicular lymphoma. In the 1600/800-mg G-CHOP arm, patients receive a cumulative dose of 7200–8000 mg, depending on the standard number of cycles delivered. In addition, the protocol has recently been amended to include GA101 at a flat dose of 1000 mg plus bendamustine (G-bendamustine) or CHOP (G-CHOP) in previously untreated patients with follicular lymphoma. Patients with a PR or CR who complete a minimum of four cycles of G-FC, six cycles of G-CHOP, or four

cycles of G-bendamustine have the option of receiving maintenance therapy with GA101 alone every 3 months for up to 2 years.

Fifty-six patients with relapsed or refractory follicular lymphoma have been enrolled in the study to receive either 6 or 8 cycles of G-CHOP every 21 days (n = 28) or 4 or 6 cycles of G-FC every 28 days (n = 28), with an additional GA101 dose administered to patients on Day 8 of Cycle 1. All 28 patients treated with G-CHOP have completed induction treatment, whereas 6 of the 28 patients who started G-FC withdrew early from induction treatment. Reasons for discontinuation of study treatment for the 6 patients who withdrew from the G-FC arm were PD for 1 patient and adverse events in 5 patients: neutropenia (3 patients), and rash and infection (1 patient each).

Overall, between the LD and HD arms, the rate of adverse events by system organ class did not differ greatly, and given the small numbers of patients, definitive conclusions cannot be drawn about differences between GA101 adverse events rates in these arms. All 56 patients experienced at least one adverse event. The most commonly reported events were classified under the system organ class “general disorders and administration-site conditions,” with the highest rate for IRR events regardless of the chemotherapy backbone and dose level group considered.

The percentage of patients with IRRs was 68% in the G-CHOP arm and 82% in the G-FC arm, with 7% of events being Grade 3 or 4 events in both chemotherapy arms. Events in the gastrointestinal disorders system organ class were the second most common reported adverse events and were reported in 86% and 71% of patients in the G-CHOP and G-FC arms, respectively. Infections and infestations events were experienced by 79% (93% HD; 64% LD) of patients in the G-CHOP arm and 57% (57% HD; 57% LD) of patients in the G-FC arm. Grade 3 and 4 infections and infestations events were reported in 21% of patients in the G-CHOP arm and 29% of patients in the G-FC arm.

Blood and lymphatic system events, with neutropenia being the most common event, were observed for 57% and 64% of the patients in the G-CHOP and G-FC arms, respectively. Of these events, 46% and 61% were considered Grade 3 or 4 events.

Neutropenic events (i.e., neutropenia, febrile neutropenia, neutropenic sepsis, and neutropenic infections) were reported in 14 patients (50%) and 17 patients (61%) in the G-CHOP and G-FC arms, respectively.

Serious adverse events were reported in 8 (29%) and 7 (25%) patients receiving G-CHOP and G-FC induction, respectively. Infections were the most commonly reported events.

No deaths have been reported during the induction treatment period.

Study GAO4753g (Phase III): GA101 in Combination with Chemotherapy

This is an open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with G-bendamustine in patients with rituximab-refractory indolent NHL.

Between April 15, 2010, and Sept 1, 2014, when the study was stopped after a pre-planned interim analysis, 396 patients were randomly assigned (194 to obinutuzumab plus bendamustine and 202 to bendamustine monotherapy).

After a median follow-up time of 21·9 months (IQR 12·1–31·0) in the obinutuzumab plus bendamustine group and 20·3 months (9·5–29·7) in the bendamustine monotherapy group, progression-free survival was significantly longer with obinutuzumab plus bendamustine (median not reached [95% CI 22·5 months–not estimable]) than with bendamustine monotherapy (14·9 months [12·8–16·6]; hazard ratio 0·55 [95% CI 0·40–0·74]; p=0·0001). Grade 3–5 adverse events occurred in 132 (68%) of 194 patients in the obinutuzumab plus bendamustine group and in 123 (62%) of 198 patients in the bendamustine monotherapy group. The most frequent grade 3 or worse adverse events were neutropenia (64 [33%] in the obinutuzumab plus bendamustine group vs 52 [26%] in the bendamustine monotherapy group), thrombocytopenia (21 [11%] vs 32 [16%]), anaemia (15 [8%] vs 20 [10%]) and infusion-related reactions (21 [11%] vs 11 [6%]). Serious adverse events occurred in 74 patients (38%) in the obinutuzumab plus bendamustine group and in 65 patients (33%) in the bendamustine monotherapy group, and deaths due to adverse events occurred in 12 patients (6%) and 12 patients (6%), respectively. Three (25%) of 12 adverse event-related deaths in the obinutuzumab plus bendamustine group and five (42%) of 12 in the bendamustine monotherapy group were treatment related.

The results of this study showed that patients receiving obinutuzumab plus bendamustine had a significant improvement in independent review committee-assessed progression-free survival compared with bendamustine monotherapy, and the median progression-free survival for obinutuzumab plus bendamustine has not yet been reached. Other efficacy parameters, such as time to new anti-lymphoma treatment and duration of response, also showed a benefi t for combination therapy compared with bendamustine monotherapy [23].

1.3.3 Pharmacokinetic and pharmacodynamic results for GA101

A population pharmacokinetic *(PK)* model has been developed for Studies BO20999 and BO21003 to characterize the pharmacokinetics of GA101 and its variability. A two-compartment model, comprising both a linear clearance pathway and a non-linear time-varying clearance pathway, was fitted to the data. Data are available for 134 patients

following intravenous (IV) administration of GA101 in Studies BO20999 (114 patients) and BO21003 (20 patients). Following infusion of GA101, the elimination appears to be characterized by clearance that is dependent on time, i.e., starting at a typical value of 594 mL/day and then gradually declining to an asymptote of 112 mL/day at steady state. Tumor burden potentially contributes significantly to the clearance of GA101, especially at the beginning of treatment when there is an excess of CD20-expressing cells. As tumor burden decreases, clearance reaches an asymptote, which was thought to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden appear to clear the drug from the plasma faster than patients with a low tumor burden as GA101 binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time since repeated treatment with GA101 is expected to reduce the number of CD20-positive tumor cells. Treatment with GA101 resulted in extensive B-cell depletion, with all patients showing a reduction in cell count to absolute zero and most reductions occurring after the first infusion. Overall, no notable increase has been observed in complement levels pre- and post-infusion, but changes have been observed in the levels of interleukin-6 and interleukin-8 before and after infusion.

2 RATIONALE OF THE STUDY

The probability to achieve CR with R-chemotherapy in patients failing a rituximab containing first line regimen is quite low. Addition of a new monoclonal antibody to the same chemotherapy should consist in an increase of response and should circumvent acquired resistence to rituximab.

3 OBJECTIVES OF THE STUDY

3.1 General objectives

Aim of this trial is to assess the efficacy and safety of new anti-CD20 antibody (GA101) in association with DHAP as induction therapy before high dose chemotherapy BEAM with ASCT in patients with relapsed/refractory DLBCL.

Primary objective is to assess whether the treatment achieves an absolute increase of the CR proportion of at least 20% (from 30% to 50%) with respect to the standard treatment with an acceptable extra-hematological toxicity grade 3-4 of 0.25 (unacceptable extra-hematological toxicity=0.40).

Secondary objectives were:

- Overall Response Rate (ORR) prior to consolidation with BEAM and ASCT
- Progression free survival (PFS) at 6 month after the end of treatment (EOT);
- Overall Survival (OS) at 2 years after the EOT;
- Feasibility and overall toxicity
- The hematopoietic cell mobilization
- The rate of patients actually proceeding to ASCT.

3.2 End-points

3.2.1 Primary endpoints

The complete response rate (CR) evaluated by PET scan after four cycles of GA101-DHAP before ASCT according to Cheson criteria [12]. Historical data with which we will compare the results of our study were obtained in the same study population but with different response evaluation criteria (Cheson criteria 1999)[13].

Severe, life-threatening, fatal (grade 3, 4 and 5) extra-hematological toxicity till one month after the last obinutuzumab administration (cycle 4) according to "Common Terminology Criteria for Adverse Events" (CTCAE), version 4.0 are defined for primary toxicity evaluation.

3.2.2 Secondary endpoints

- Overall response rate (ORR): a patient is defined as a responder if she/he has a complete or partial response, evaluated by PET/TC, after four cycles of GA101-DHAP
- Progression free survival (PFS): measured from the date of starting salvage therapy to the date of disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow up will be surveyed at their last assessment date.
- OS: measured from the date of starting salvage therapy to the date of death from any cause. Patients alive at the time of the final analysis will be surveyed at the date of the last contact. For both PFS and OS minimum follow up time required for all patients will be 2 years.
- Overall Toxicity: severe, life-threatening, fatal (grade 3, 4 and 5) and/or serious adverse events are defined according to "Common Terminology Criteria for Adverse

Events" (CTCAE), version 4.0. and adverse events of special interests (AESI), evaluated up to 6 months from the end of autologous transplantation.

- Mobilizing potential: amount of CD34 + stem cell collected /Kg
- Proportion of patients successfully completing ASCT

4 PATIENT SELECTION CRITERIA

Patients with DLBCL who failed or relapsed after one previous chemotherapy regimen will be enrolled. The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

The following items are generally used in the definition of selection (eligibility) criteria:

4.1 Inclusion criteria

1. 18≥ Age < 65
2. Relapsed/refractory disease after receiving one line of standard R-CHOP like chemotherapy
3. Diffuse Large B-cell Lymphoma at relapse. The re-biopsie is particularly recommended if relapse is over 1 year from previous complete remission. If this is harmful for the patient, the patient can be enrolled if archivial tumor sample and block from first diagnosis are available.
4. Measurable and/or evaluable disease
5. Any Ann Arbor stage and IPI group at relapse
6. Performance status $\leq$ 2 according to ECOG scale unless due to lymphoma
7. No Central Nervous System (CNS) disease (meningeal and/or brain involvement by lymphoma)
8. Adequate haematological counts: ANC $\geq$ 1.5 x 10^9/L, Hgb $\geq$ 10.5 g/dl (transfusion independent), Platelet count > 75 x 10^9/L (transfusion independent), with the exception of cytopenia due to lymphoma bone marrow involvement
9. Normal liver function (ALP, AST, ALT, GGT, conjugated bilirubin total < 2 x ULN) if not related to lymphoma
10. Normal kidney function (creatinine clearance $\geq$ 80 ml/min)
11. Cardiac ejection fraction $\geq$ 50% (MUGA scan or echocardiography)

12. Normal lung function
13. Absence of active infections
14. Non peripheral neuropathy or active neurological non neoplastic disease of CNS
15. Non major surgical intervention prior 3 months to randomization if not due to lymphoma and/or not other disease life-threatening that can compromise chemotherapy treatment
16. Disease free of prior malignancies other than lymphoma for > 3 years with exception of currently treated squamous cell and basal cell carcinoma of the skin or carcinoma in situ of the cervix or breast
17. Life expectancy > 6 months
18. No psychiatric illness that precludes understanding concepts of the trial or signing informed consent
19. Written informed consent
20. Women must be:
    - postmenopausal for at least 1 year (must not have had a natural menses for at least 12 months)
    - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy),
    - abstinent (at the discretion of the investigator/per local regulations), or
    - if sexually active, be practicing a highly effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study. They must also be prepared to continue birth control measures for at least ~~12~~ 18 months after terminating treatment.
21. Women of childbearing potential must have a negative serum or urine beta-human chorionic gonadotropin (beta-hCG) pregnancy test at screening
22. Men must agree to use an acceptable method of contraception (for themselves or female partners as listed above) for the duration of the study. Men must agree to use

a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug.

4.2 Exclusion criteria

1. Diagnosis of Lymphoblastic Lymphoma, Burkitt Lymphoma, Non Hodgkin Lymphoma CD20 negative, Mantle Cell Lymphoma, Follicular Lymphoma, Primary Mediastinal Lymphoma
2. Age ≥ 65 years
3. Patients ineligible to high-dose chemotherapy
4. Performance status > 2 according to ECOG scale if not due to lymphoma
5. Patients who previously received GA101 (obinutuzumab) are excluded.
6. Patient has known or suspected hypersensitivity or intolerance to Rituximab
7. Patient has received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non treatment studies is allowed, if it will not interfere with participation in this study.
8. CNS disease (meningeal and/or brain involvement by lymphoma)
9. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances
10. Positive test results for chronic hepatitis B infection (defined as positive HBsAg serology). Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.
11. Positive test results for hepatitis C (HCV antibody serology testing). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
12. Known history of HIV seropositive status. For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
13. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug

14. Uncontrolled or severe cardiovascular disease including myocardial infarction within six months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
15. Cardiac ejection fraction < 45% (MUGA scan or echocardiography)
16. Creatinine clearance < 45 ml/min
17. Presence of major neurological disorders
18. Active infection
19. Major surgical intervention prior 3 months to randomization if not due to lymphoma and/or other disease life-threatening that can compromise chemotherapy treatment
20. Prior malignancies other than lymphoma in the last 3 years with exception of currently treated squamous cell and basal cell carcinoma of the skin or carcinoma in situ of the cervix or breast
21. Life expectancy < 6 months
22. Any other coexisting medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent.
23. If female, the patient is pregnant or breast-feeding.

5 STUDY DESIGN

This is a prospective, multicenter, single arm, phase II trial in young patients (18-65 years) affected by relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) at diagnosis, eligible to high-dose therapy.

Aim of the study is to assess whether the addition of GA101 to DHAP is more promising than standard R-DHAP, as induction therapy before high dose chemotherapy BEAM with ASCT with respect to response and safety.

After providing written informed consent, patients will be evaluated for eligibility during a 21-day screening period. If they continue to meet eligibility criteria they will receive the first dose of GA101-DHAP.

The main efficacy variable will be the response to treatment, defined as the incidence of complete response assessed by PET-scan after 4 cycles of chemotherapy. The proportion of complete response will be the principal measure of efficacy. Study discontinuation

because of death or worsening conditions will be considered as failures and included in the estimation of response rates.

All toxic reactions will be annotated and their grade will be assessed according to the Common Toxicity Criteria (CTC) Version (see appendix). The proportion of non-hematologic toxicity (of grade 3 or greater) and of the patients not mobilizing enough peripheral stem cells for ASCT will be the principal measure of safety. All patients given at least one dose of the experimental treatment will be included in the estimation of toxicity rates. During the treatment period of four cycles, all patients will receive a total of four 28-day courses of chemotherapy.

Duration of treatment will be 4 months (one cycle per-month) plus 30 days for response evaluation.

During the study, disease status will be evaluated after the 4^{th} cycle by imaging test (18FDG-PET and CT scan), and a CT after 2^{nd} cycle.

Adverse events will be monitored from the first study-related procedure, throughout treatment, and for 30-42 days (i.e., until the End of Treatment Visit before high dose chemotherapy). National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) will be used to record the intensity (severity) of adverse events.

Serious adverse events will be reported as described.

Procedures to be performed during the study are summarized on the Appendix, Time and Events Schedule.

5.1 Rationale for the Study Design

The study is designed primarily to evaluate the efficacy and safety of GA101-DHAP in patients with DLBCL who have relapsed or are refractory to one chemotherapy regimen and secondarily to assess safety and capability to mobilize peripheral stem cells. The study is designed with two stages and with stopping rules after the first stage. In particular, at the end of the first stage, the study will be stopped if the efficacy is too low or if the toxicity, measured during the drug administration period, is too high with respect to pre-defined thresholds.

6 STATISTICAL CONSIDERATIONS

6.1 Statistical design

This is a prospective, multicenter, single arm, two stage phase II trial designed to assess whether the addition of GA101to DHAP will show a favorable efficacy and safety profile in comparison with standard R-DHAP as induction therapy before high dose chemotherapy BEAM with ASCT in terms number of CR. Historical data with which we will compare the results of our study were obtained in the same study population but with different response evaluation criteria [13].

6.1.1 Sample size, study duration and stopping rules

The principal aim of the study is to test whether the efficacy of the experimental induction therapy is better than standard ones in determining a CR and warrants further investigation. According to the Briant and Day[24] two-stage design for a phase II clinical trial, with an alpha error=0.05, a beta error=0.15, an unacceptable response proportion of 0.30 and an acceptable response of 0.50 and with an alpha error=0.10 an acceptable toxicity of 0.25 and an unacceptable extra-hematological toxicity grade 3-4 of 0.40, the sample size of the first stage is 29. At the end of the first stage the study will be stopped if the number of patients with a CR is <10/29 or the number of patients who do not experience toxicity is less than 19/29. With 10 or more CR out of the first 29 patients and with 19 or more patients that do not experience extra-hematological toxicity grade 3-4 the study will proceed to the second stage until a total sample size of 78 patients is reached. For toxicity evaluation all types of extra-hematological toxicity grade 3-4 emerging till one month after the last obinutuzumab administration (cycle 4) will be considered. At the end of the study, the experimental induction therapy will not be considered worthy for further investigation if the total number of CR is less than 31 or the total number of patients who do not experience extra-hematological toxicity grade 3-4 is less than 52.

Safety analyses for extra-hematological toxicity grade 3-4 will be also performed at the end of each patient's treatment in order to better evaluate the safety profile.

The overall hematological and extra-hematological toxicities will be also described and evaluated up to 6 months from the end of autologous transplantation, but they are not part of the definition of stopping rules.

The expected study duration is 88 months (52 for enrollment and 36 for the follow-up). The accrual of 78 patients is expected to be reached in 52 months allowing for a period of temporary study closure at the end of the enrollment of the 29 patients of the first stage).

6.1.2 Statistical analysis

The main efficacy and safety statistical analyses will be based on all enrolled patients (the intention-to-treat – ITT- population). A detailed safety analyses will be based on all patients receiving at least one dose of the experimental treatment.

All dichotomous endpoints (response, toxicity, ASCT feasibility) will be estimated using proportions and corresponding 95% confidence intervals.

ASCT feasibility will be evaluated as the proportion of patients successfully completing ASCT.

Survival probabilities for time to event endpoints (PFS, OS), will be estimated with the Kaplan Meier method.

Exploratory analyses on the prognostic role of biological markers on response and on PFS/OS will be performed using the logistic and the Cox proportional Hazard models, respectively. According to response and toxicity all biological markers will be measured at the end of induction treatment (GA101-DHAP) from +30 to +45 days, according to PFS/OS they will be measured after ASCT completion from +60 to + 90 days.

7 PATHOLOGICAL REVIEW

A centrally pathological review is planned at accrual for all patients enrolled into the trial; investigator centers will make available the archival tumor samples taken:

- at first diagnosis, if re-biopsy at relapse is not available;
- at relapse if available.

A re-biopsy at relapse is not mandatory at study entry, but recommended for patients relapsed at a certain distance from the initial therapy (> 1 year).

Re-biopsy at relapse is mandatory at study entry for all patients with superficial adenopathy.

The central revision will be perfomed by a panel of pathologists expert in DLBCL diagnosis and responsible of trial revision. Central revision will primarily concern the confirmation of the original diagnosis and the subdivision of DLBCL into Germinal Center Cell or non-Germinal/Activated-B-cell according to the most commonly used algorithms[25,26].

Immunohistochemistry panel: CD5, CD20, CD10, BCL6, IRF4, CD30, BCL2, MYC, Ki-67

8 STUDY TREATMENT

Patients receive:

- GA101-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + GA101-DHAP x 2, restaging with PET evaluation and consolidation with BEAM/FEAM and ASCT in responsive patients (CR + PR)

8.1 Rationale for GA101 Dose

PK analyses of the GA101 Phase I studies, together with published data on rituximab (Daydé et al. 2009), demonstrate that patients with higher disease burden have a faster antibody clearance. Although dosing according to target volume is difficult, these data suggest that patients with high tumor burden may require higher doses to saturate the target. This finding was further substantiated by modeling and simulation experiments, which showed a higher degree of clearance variability observed at lower GA101 doses.

To further understand a potential dose effect, in the Phase II part of Study BO20999, patients were randomized to two different GA101 dose cohorts. In the LD cohort, patients received 8 cycles of 400 mg of GA101, with an additional 400-mg dose given on Day 8 of the first cycle. In the HD cohort, GA101 was given at 1600 mg on Days 1 and 8 of the first cycle, followed by 800 mg at Cycles 2–8. Cumulative doses were 3600 mg and 8800 mg in the LD and HD cohorts, respectively. In comparison, a typical dose for the reference antibody rituximab is approximately 5000–6000 mg (8×375 mg/m^2), which would be in between the low and high doses tested for GA101. PK simulations show that the 95% confidence limits for exposure are between the low and high doses and are not overlapping. No dose-limiting toxicities were observed across the two doses and, although there was a slight increase of IRRs and neutropenia rates in the HD cohort, GA101 was generally very well tolerated. As expected, PK variability was lower at the higher dose. Importantly, increased overall response rate have been observed in the HD cohort compared with those in the LD cohort (55% vs. 13%, respectively) in the subset of patients with indolent lymphoma. Findings in the aggressive lymphoma cohort did not show a marked difference in response rates between patients receiving the high and low doses (32% and 24%, respectively), yet this cohort was further subdivided by the inclusion of patients with relapsed DLBCL and relapsed MCL and small numbers (25 patients with DLBCL and 15 patients with MCL) might have prevented a more compelling result.

In summary, it was concluded that a higher dose—1000 mg—of GA101 can be delivered intravenously and that the available evidence from nonclinical studies, PK studies, modeling and simulation, and clinical trials (Phase I and Phase II) in patients with NHL are suggestive of a higher dose being more appropriate to saturate the target in the majority of patients with NHL irrespective of their tumor load and, thus, more efficacious than a lower dose.

8.2 Scheme GA101-DHAP

GA101-DHAP scheme could be performed as in-patient or out-patient due to different organizational needs. No differences are reported in literature in term of efficacy of the two schemes [27,28]

In-patient version

- GA101 1000 mg iv day 1, 8, 15 on first cycle (starting from cycle 2, GA101 1000 mg day 1)
- Cisplatin 100 mg/sqm iv day 1 of every cycles in 24-hours infusion
- Cytarabine 2000 mg/sqm in 3-hours infusion every 12 hours iv day 2 of every cycles
- Dexametasone 40 mg day 1-4 of every cycles
- Pegfilgrastim 6 mg sc single dose 24 hours after the end of chemotherapy or G-CSF from day 4 till stem cell harvest during mobilization's course (II o III cycle GA101-DHAP)
- GA101 1000 mg iv 24 hours before apheresis as purging in vivo during second courses of therapy

Out-patient version

- GA101 1000 mg iv day 1, 8, 15 on first cycle (starting form cycle 2, GA101 1000 mg day 1)
- Cisplatin 100 mg/sqm iv day 1 of every cycles in 3-hours infusion
- Cytarabine 2000 mg/sqm in 3-hours infusion iv day 2 and day 3 of every cycles
- Dexametasone 40 mg day 1-4 of every cycles
- Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II or III cycle GA101-DHAP)
- GA101 1000 mg iv 24 hours before apheresis as purging in vivo during second courses of therapy

8.2.1 GA101

a) Formulation

GA101 is provided as a single-dose, sterile liquid formulation in a 50-mL pharmaceutical grade glass vial containing a nominal 1000 mg of GA101 (G3 material). The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill). For further details, see the GA101 Investigator's Brochure.

b) Handling and Storage

The recommended storage conditions for the GA101 drug product are between 2°C and 8°C protected from light. Chemical and physical in-use stability for GA101 dilutions in 0.9% sodium chloride (NaCl) have been demonstrated for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting. The prepared diluted 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°C–8°C. GA101 should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in-line filter because of potential adsorption. For further details, see the GA101 Investigator's Brochure.

c) GA101 Dose and Schedule

GA101 will be administered by IV infusion as an absolute (flat) dose of 1000 mg on Day 1 of each 28-day cycle for 4 cycles. GA101 will be administered prior to DHAP, and patients should be observed 30 minutes prior to starting DHAP. If DHAP is not started or completed on Day 1 because of the long duration of GA101 therapy, DHAP chemotherapy may be administered on Day 2. During Cycle 1, GA101 will also be infused on Days 8 and 15.

d) GA101 Preparation

GA101 drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl to the final drug concentration of 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the sodium chloride. Withdraw 40 mL of GA101 from a single glass vial and inject into the infusion bag (discard any unused portion of GA101 left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

Administration sets with polyvinyl chloride (PVC), polyurethane (PUR), or polyethylene as product contact surface and IV bags with polyolefine, polypropylene (PP), PVC, or polyethylene, as product contact surface are compatible and may be used.
Do not use GA101 beyond the expiration date stamped on the carton.

e) GA101 Administration

GA101 should be administered to patients in a clinical setting (inpatient or outpatient), where full emergency resuscitation facilities are immediately available and patients should be under close supervision of the investigator at all times. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, access (either through an IV line or central venous catheter) should remain in place for at least 1 hour from the end of infusion, and if no adverse events occur after 1 hour, the IV access may be removed.
Instructions for the first and subsequent infusions of GA101 are presented in Table 1.

Table 1

Administration of First and Subsequent Infusions of GA101

First Infusion (Day 1)	Subsequent Infusions
Begin infusion at and initial rate of 50 mg/hr. If no infusion reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.	If a patient experienced an infusion reaction during the prior infusion, start at the same rate as the first infusion (50 mg/hr) and follow directions as noted. If the patient tolerated the prior infusion well *(defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr)*, begin the infusion at a rate of 100 mg/hr. If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in

	rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.

GA101 should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of GA101. Do not administer as an IV push or bolus.

On days when both GA101 and DHAP are given, GA101 will be administered prior to DHAP and patients should be observed 30 minutes prior to starting DHAP. DHAP chemotherapy may be administered the next day if it cannot be given on the same day as GA101 administration. Prior to each GA101 infusion that is given in combination with DHAP, patients should take the Day 1 the premedication for each cycle of the DHAP regimen (Tab 1).

Table 2

Premedication to be administered before Obinutuzumab infusion to reduce the risk of Infusion Related Reactions (recommended for ALL patients).

Day of Treatment Cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histaminic drug[3]	
Cycle 1: Day 2	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histaminic drug[3]	
Cycle 1: Day 8, Day 15	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
Cycles 2-6: Day 1	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic drug[3]	

[1] 100 mg prednisone/prednisolone or 20mg dexamethasone or 80mg methylprednisolone Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

[2] e.g. 1000 mg acetaminophen/paracetamol

[3] e.g. 50 mg diphenhydramine

For patients with a high lymphocyte count or bulky lymphadenopathy, the infusion may be given extremely slowly over a longer period of time, or the dose may be split and given over more than one day.

If a patient does not experience a IRR (grade 1 or more) during the first infusion, the premedication for a subsequent infusions can be omitted.

For more detailed nonclinical information about GA101, please refer to the current version the Investigator's Brochure.

8.3 Mobilization and apheresis

Mobilization after II or III cycle (only in case of bone marrow positivity at relapse) of GA101-DHAP, with GA101 pre-apheresis; recommended harvest of at least $3x10^6$ cells CD34+/kg.

If at relapse or progression the bone marrow biopsy was positive, after the second cycle a new biopsy was necessary to define negativization and to schedule apheresis after the third cycle.

8.4 BEAM or FEAM + ASCT

- BCNU 300 mg/sqm iv day -7 (BCNU can be replaced with Fotemustine 300 mg/sqm)
- Cytarabine 200 mg/sqm every 12 hours iv days -6, -5, -4, -3 (8 total doses)
- VP-16 100 mg/sqm every 12 hours iv days -6, -5, -4, -3 (8 total doses)
- Melphalan 140 mg/sqm iv day -2
- Reinfusion of PBSC (CD34+ > 3 x10^6/Kg) day 0
- Pegfilgrastim 6 mg sc day + 1

8.5 Risks Associated with GA101 Therapy

No evidence available at the time of the release of this protocol indicates that special warnings or precautions are appropriate, other than those noted in the GA101 Investigator's Brochure and as described in the following sections.

8.5.1 Infusion-Related Reactions and Hypersensitivity Reactions (Including Anaphylaxis)

To date, the commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, and fatigue, as well as other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE, v3.0, Grade 1 and 2 events), and $<$ 10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished; the events resolved with slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

8.5.2 Tumor Lysis Syndrome

Cases of tumor lysis syndrome have been reported with GA101 administration. To date, no patient has required hemodialysis for renal failure. Patients with a high tumor burden, including patients with a lymphocyte count $\geq 25 \times 10^9$/L (particularly patients with B-cell CLL and MCL), are at increased risk for tumor lysis syndrome and severe IRRs.

8.5.3 Thrombocytopenia and Neutropenia

Cases of Grade 3 or 4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with GA101 administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. Use of granulocyte colony-stimulating factors (G-CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary–prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥ 60 years old and/or with co-morbidities (Lyman et al. 2004). The use of G-CSF is strongly recommended in all patients treated with G-CHOP.

8.5.4 Infection

Based on its anticipated mode of action, resulting in profound B-cell depletion, GA101 may be associated with an increased risk of infections. Infections have been reported in patients receiving GA101. Therefore, GA101 should not be administered to patients with active severe infections.

Reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, *Varicella zoster* virus, herpes simplex virus, *John Cunningham* virus (JC*V*), and hepatitis C virus) that were new, reactivation, or exacerbation, have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. The risk of such infections with GA101 is unknown. Particular attention should be given to patients who have previously received significant immunosuppressive treatment such as high-dose chemotherapy and stem-cell transplant.

Cases (including fatal) of JCV infection that resulted in progressive multifocal leukoencephalopathy (PML, destructive infection of oligodendrocytes of the CNS white matter) have been reported in patients treated with anti-CD20 therapies, including GA101.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are very unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with GA101 should be withheld during the investigation of potential PML and permanently discontinued in case of PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

There may also be potential health risks, including unknown risks derived from exposure to GA101.

8.5.5 Dose- adjustment for GA101

No dose modifications of GA101 (1000 mg) are allowed.

If administration of chemotherapy is delayed, there will be no dose modification of GA101, and the administration of GA101 and all chemotherapy drugs should be delayed for the same time frame, e.g., if DHAP therapy is delayed, administration of GA101 should also be delayed so that they are given on Day 1 of the same cycles.

8.5.6 Dose delay for GA101 on Cycle 1 Day 8 and Cycle 1 Day 15

Guidelines for dose delay on Cycle 1 Day 8 and Day 15.

Event(s)	Dose Delay or Modification
Febrile neutropenia or neutropenia with infection	Hold GA101 dose until it resolves If Cycle 1 Day 8 is delayed long enough that you are approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or neutropenic fever has resolved) If Cycle 1 Day 15 is delayed long enough that you are approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of GA101+ DHAP as scheduled (if infection or fever has resolved) Note: GA101 should not to be held for asymptomatic neutropenia
Severe thrombocytopenia (platelets < 10,000/μL) and/or	Hold GA101 only in case of severe thrombocytopenia (platelets < 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves

symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet ihibitors	If Cycle 1 Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved) If Cycle 1 Day 15 is delayed then skip Day 15 dosing and administer Cycle 2 Day 1 of GA101 + DHAP as scheduled (if symptomatic bleeding has resolved)
Thrombocytopenia with platelets < 20,000/µL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet ihibitors [a, b]	Hold GA101 only in case of platelets < 20,000/µL or (irrespective of platelet count) until it resolves. If Cycle 1 Day 8 is delayed then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved) If Cycle 1 Day 15 is delayed then skip Day 15 dosing and administer Cycle 2 Day 1 of GA101 + DHAP as scheduled (if symptomatic bleeding has resolved). For patients who are receiving LMWH, when thrombocytopenia with platelets < 20,000/µL develops, reduce the dose of LMWH used [b] For patients who are on platelet inhibitors, when thrombocytopenia with platelets < 20,000/µL develops, consider temporarily holding their use [b]

[a] If the clinical condition of the patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets < 20,000/µL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1, Day 1.
[b] Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk

8.5.7 Dose- adjustment for DHAP

Before each course FBC will be taken and, if at day 28 ANC <1500/mm^3 and/or platelets <100.000/mm^3, the whole regimen will be delayed by one week. If at day 35 the ANC is >1000-1500/mm^3 and/or PLT 75-100.000/mm^3 the dosage of each chemotherapeutic drug will be reduced at 75%. If FBC has not recovered one further delay-week is admitted.
If at day 42 ANC are still <1000//mm^3, and/or platelets < 75.000/mm^3, the patient will go off-study.

9 WITHDRAWAL

From GA101 perspective, patients must discontinue study drug if they experience any of the following:

- Pregnancy
- PML
- Grade 4 IRR

Patient should be withdrawn immediately and treatment must be discontinued permanently.

- Grade 3 IRR at re-challenge despite adequate premedication: patient must be withdrawn immediately and treatment must be discontinued permanently

- Grade 3 or 4 hematological toxicity that has not resolved to Grade ≤ 2 and requires to delay treatment by more that 14 days (Thrombocytopenia needs to resolve to Grade ≤ 1)
- Grade ≥ 2 non-hematological toxicity that does not resolve to Grade ≤ 1/baseline and requires to delay treatment by more that 14 days
- Hepatitis B reactivation

9.1 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states his/her wish not to contribute further data to the study, the assigned FIL Study Coordinator should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. Data of the patient will or won't be kept in the data base, according to patient's wish and regulatory requirements.

9.2 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time site investigator must document attempts to contact the patient either by phone or letter.

10 CONCOMITANT TREATMENT

10.1 Recommended concomitant treatments

During treatment are recommended as concomitant therapy:

- Pegfilgrastim 6 mg sc, 24 hours after the end of chemotherapy or G-CSF from day 5 till neutrophil recovery or till stem cell harvest during mobilization's course (II or III cycle GA101-DHAP)
- Cotrimoxazole BACTRIM 3 tablets/week (or 1 x 2/day per two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase
- In patients with Ab antiHBcAg +, Ab antiHBsAg +/- prophylaxis against hepatitis B

reactivation with Lamivudine 100 mg from one week prior the start of the treatment to one year after the end of the treatment

- Antimicrobial prophylaxis is strongly recommended, if necessary
- All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated
- All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted

10.2 Permitted concomitant therapy

The following medications and support therapies that may be used if needed during this study:

- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy is strongly recommended in patients with herpes virus infection reactivation
- Additional prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole will be administrated in case of neutropenia <1.0 x 109/l.
- Mozobil- Plerixafor in addition to GSCF during mobilization was permitted
- Immunoglobulin assay is advisable once a month during the therapy with immunoglobulin replacement in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events.
- Platelets and red blood cell transfusion are allowed, if needed. Packed red cells and platelets transfusions will be given with filtered and irradiated products in case of Hb < 8 g/dL or Plts < 10 x 109/L.
- Erytropoietin therapy is allowed according to ASH/ASCO guidelines.
- Bowel care is recommended to prevent constipation and should be administered per standard practice.
- Antiemetic agents.
- Premedication for GA101 infusion should be considered before each infusion of rituximab, because it may reduce infusion reactions, according to Tab 1.

10.3 Prohibited concomitant therapy

The following medications and supportive therapies are prohibited at all times:

- Any antineoplastic agent other than those planned by the study program.
- Any experimental agent.

10.4 Females of childbearing potential

The patient has to use a contraceptive during the course of the treatment and for 30 days after completion of therapy. The accepted methods of contraception include: coil (IUD), hormonal contraceptives (pill, injection or implant), condoms, diaphragm, tubal ligament, vasectomies (in men) or complete abstinence.

10.5 Male subjects

If the partner of the patient is a woman of childbearing age has to use a contraceptive during the course of the treatment and for 30 days after completion of therapy. The accepted methods of contraception include: coil (IUD), hormonal contraceptives (pill, injection or implant), condoms, diaphragm, tubal ligament, vasectomies (in men) or complete abstinence.

11 CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

11.1 Staging evaluation, baseline

Baseline assessment must be performed during 30 days before starting therapy.

- Complete medical history, ECOG performance status, physical examination
- ECG and echocardiogram or MUGA scan for LVEF evaluation
- Complete blood count, hematology workup and biochemistry (dosage serum Ig)
- Serum virology (HBsAg, HBcAb, HCV and HIV serology)
- Lymph-node or tissue biopsy for histological diagnosis and shipment of paraffin block for centrally pathology review and for pathological studies
- GC/ABC value on diagnostic tissue
- Aspirate and bone marrow biopsy
- Diagnostic Lumbar Puncture for determination of cell count, differential, cytologic and cytoflussimetry examination (if possible) of tumor cells; in patients with clinical suspect of CNS involvement, according to SIE criteria
- CT scan neck, chest, abdomen and pelvis
- Total body PET scan (recommended)
- Other assessment: RMN brain/column, endoscopy, ORL visit, etc. according to physician judge and if clinically relevant
- Pregnancy test (if applicable)

- Written informed consent

11.2 Valuation at each GA101-DHAP corse

- Blood count and complete workup with biochemistry (dosage serum Ig at the end of the cycle 4), physical examination and hematological and extrahaematological toxicity evaluation the day before or day 1 of therapy and between two cycles and during aplasia phase (recommended at day +8-12-16-20 and/or till granulocytes and platelets recovery)

11.3 Intermediate response evaluation

The evaluation of intermediate response will be assessed after 2 courses of GA101-DHAP.

- ECOG performance status, physical examination
- Blood count and complete workup with biochemistry
- Aspirate and bone marrow biopsy (if positive at baseline), necessary to schedule the apheresis
- CT scan neck, chest, abdomen and pelvis
- Total body PET scan (recommended, not mandatory)

Responsive patients (in partial or complete response) after two cycles of therapy, will continue the trial and will be treated with two further courses of GA101-DHAP as planned. Patients with progressive disease or stable disease after the first two cycles of therapy will stop treatment and will be considered as failure.

11.4 Pre-ASCT evaluation - end of treatment

The evaluation of pre-ASCT response will be assessed after 4 courses of Ga101
-DHAP:

- ECOG performance status, physical examination
- Blood count and complete workup with biochemistry
- Aspirate and bone marrow biopsy (if positive at baseline)
- CT scan neck, chest, abdomen and pelvis
- PET total body (mandatory)

Patients in complete remission after four cycles of therapy, will continue the trial and will be

treated with BEAM + ASCT as planned.

Patients in partial remission after four cycles of therapy, will continue the trial and will be treated with BEAM +ASCT at investigator discretion.

Patients in progression disease or stable disease after the first two cycles of therapy stopped treatment and will be considered failure.

11.5 Post –ASCT evaluation

Final evaluation will be performed two months after the end of BEAM + ASCT.

- ECOG performance status, physical examination
- Blood count and complete workup with biochemistry
- Aspirate and bone marrow biopsy (if positive at baseline)
- CT scan neck, chest, abdomen and pelvis
- PET total body (mandatory)

Complete response, Partial response or no response will defined according to Cheson 2007 response criteria.

11.6 Follow-up

Every three months during the first two years after chemotherapy and then every 4-6 months in the third year after chemotherapy, will be evaluated:

- ECOG performance status, physical examination
- Blood count and complete workup with biochemistry

Every 6 months during the first two years after chemotherapy (at month 6-12-18-24) will be evaluated:

- CT scan neck, chest, abdomen and pelvis

12 FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING

The web study area, with a dedicated database, the electronic Case Report Form (CRF) and all the required functions, will be developed through the FIL website (http://www.filinf.it).

All participating centers will receive a password to access the internet-based database.

Several systematic quality controls will be active during data entry; periodic statistical checks and personalized queries will be performed during the study.

Frequency of on-site monitoring will be planned according to the results of the statistical quality controls.

13 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and are mandated by regulatory agencies worldwide.

13.1 Definitions

Adverse Event Definitions and Classifications

13.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to the medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

The Adverse Events collection for each subject will start with the signing of informed consent form.

13.1.2 Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening

(the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect
- other medically important condition: would be any important medical or clinical event that may not be immediately life-threatening or result in a fatality or hospitalization but that may jeopardize the patient or require intervention to prevent another outcome e.g significant/persistent disability, life-threatening reaction congenital anomaly. Examples of such potentially serious events (according to medical judgment) include a suspected transmission of infections agent by a medicinal product, allergic bronchospasm, blood dyscrasias or convulsion, development of drug dependency or drug abuse, cancer. Whether the event should meet one of these requirements, please report into the category “Other Medically Important Condition” on the SAE form.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Adverse events of special interest (AESI)

The following types of events are considered to be AESIs due to their observed frequency and/or clinical relevance:

- SAE associated with obinutuzumab infusion (defined as any treatment-related AEs occurring during or within 24 hours of an obinutuzumab infusion and related to obinutuzumab)
- Serious infections
- Serious neutropenia
- Tumor lysis syndrome (TLS)
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

13.1.3 Unlisted (Unexpected) Adverse Event

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product with a marketing authorization, the expectedness of an adverse

event will be determined by whether or not it is listed in the summary of product characteristics (SmPC).

13.1.4 Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 1.2.

13.1.5 Product Quality Complaint

A product quality complaint (PQC) is defined as a complaint specific to the product itself, its supporting devices or packaging, as opposed to its effect on the patient. Examples include damaged or missing tablets; wrong strength or color of tablets; damaged packaging; a label that cannot be read; a liquid that should be clear but is cloudy or contains unexpected particles; a bent needle; a broken syringe; a missing patient information leaflet, or the identification of a potentially counterfeit medicine.

13.2 Attribution Definitions

13.2.1 Intensity (Severity) Reporting and Attribution

For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each adverse event will be determined by using Version 3.0 of the National Cancer Institute Common Toxicity Criteria (NCI CTC) as a guideline (homepage http://ctep.info.nih.gov), wherever possible. The criteria will be provided to the investigator as a separate document. In those cases where the NCI CTC do not apply, intensity should be defined according to the following criteria:

- Mild: Awareness of sign or symptom, but easily tolerated, causing minimal discomfort and not interfering with everyday activities; no medical intervention/therapy is required.
- Moderate Discomfort: Enough to cause mild to moderate interference with normal daily activities, some assistance may be needed, no minimal medical intervention/therapy is required.
- Severe: Extreme distress causing significant impairment of functioning or incapacitation and inability to perform normal daily activities. Some assistance is usually required; medically intervention/therapy is required and hospitalization may be required

- Life Threatening: Extreme limitation in activity. Risk of death from the reaction as it occurred.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

Relationship to study drug administration will be determined as follows:

- Not related

  An adverse event which is not related to the use of the drug.
- Unlikely/Doubtful

  An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- Possible

  An adverse event which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- Probable

  An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- Definite/Very Likely

  An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

13.3 Reporting Procedures

All Adverse Events

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs regardless of relationship to study drug, should be reported until the Final Response Assessment. Grade 3 and 4 infections should be reported until 24 months after EOT Visit.

After the end of the study, all SAEs, non-serious AESIs (regardless of causality), late onset neutropenia, and secondary malignancies occurring to a patient after the treatment of that patient has ended, should be reported to the Sponsor if the investigator becomes aware of them. Grade3–5 infections should be reported for up to 2 years after the end of the study and all related SAEs indefinitely.

The investigator is not required to actively monitor patients after the study has ended.

All adverse events will be registered in CRF from the time a signed and dated informed consent form is obtained until 30 days after the administration of the last dose of study drug. Those meeting the definition of serious adverse events must be reported using the Serious Adverse Event Form.

Serious Adverse events occurring after 30 days should be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding the study drug (dose change, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade, the most abnormal value observed during the adverse event, and the value supporting recovery to Grade 0 or 1 or to baseline condition.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor-Investigator instructions.

The Sponsor-Investigator assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor-Investigators will also report to the Investigator, Independent Ethics Committee/Institutional Review Board (IEC/IRB) and to the Italian Drug

Agency (AIFA) all serious adverse events of this study that are unlisted and associated with the use of the drug.
Subjects must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

Pregnancies

While pregnancy, in itself, is not an adverse event, any subject pregnancy or pregnancies in partners of male subjects included in the study must be submitted by investigational staff to the Sponsor-Investigator within 24 hours of their knowledge of the event using the pregnancy notification form.
Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.
Because the study drug may have an effect on sperm, or if the effect is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form.
Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Serious Adverse Events and/or Pregnancies and/or Product Quality Complaint

All SAEs (and/or Pregnancies and/or PQC and/or non serious AESIs) occurring during clinical studies must be reported to the appropriated Sponsor-Investigator’s contact person by investigational staff within 24 hours of their knowledge of the event.
Information regarding SAEs (and/or Pregnancies and/or PQC) will be transmitted to the Sponsor-Investigator using the Serious Adverse Event Form (and/or the Product Quality Complaints Form), which must be signed by a member of the investigational staff. It is preferable that serious adverse events be reported via fax. Subsequent to a telephone report of a serious adverse event (and/or a Pregnancy and/or a PQC), a Serious Adverse Event Form (and/or a PQC form) must be completed by the investigational staff and transmitted to the Sponsor-Investigator within 1 working day.
The SAE(s) and/or Pregnancy report(s) and/or PQC must be sent to the Sponsor-Investigator Pharmacovigilance Contact Person to the following fax number:

Sponsor contact:

Dr. Alessandro Levis

Address: Segreteria Fondazione Italiana Linfomi ONLUS c/o Ematologia Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo via Venezia 16, 15121 Alessandria

Phone no.: +39-0131-206129

Fax no.: +39-0131-263455

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for:

- social reasons in absence of an adverse event
- surgery or procedure planned before entry into the study (must be documented in the CRF)
- study drug administration
- study related procedures defined in the protocol.

Inbound reporting process by the Sponsor-Investigator to Roche

The Sponsor-Investigator is responsible for checking the completeness of SAE (and/or Pregnancy and/or PQC) information, both for the initial report and for follow-up and for sending a copy of all SAE (and/or Pregnancy and/or PQC) information to Roche Local Safety Officer (LSO) as agreed in the Safety Data Exchange Agreement (SDEA).

If any clarification regarding SAE/Pregnancy/PQC reported is needed, the Sponsor-Investigator will receive a query by e-mail from the Roche LSO and he will be then responsible for forwarding it to the appropriate site.

The satellite site will reply to the query and will send it back to the Sponsor-Investigator who is then responsible for forwarding the answer to Roche LSO within 24 hours.

Reconciliation

Reconciliation between Sponsor and Roche LSO of serious adverse event and Pregnancy listing will be every three months. The Sponsor-Investigator is then responsible for initiating corrective actions if needed.

14 ETHICAL CONSIDERATIONS

14.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) (“IEC”).

15 SUBJECT IDENTIFICATION – PERSONAL DATA PROTECTION

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number

will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a “key” kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection (“privacy”) regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see paragraph 14.3 below). Such information must (i) identify the roles of the holder (“titolare”) and processor (“responsabile”, appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient’s prior and specific consent to such processing.

Patient information or documentation may be considered “anonymous”, and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

15.1 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

16 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

17 DATA OWNERSHIP

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Sponsor's prior express consent.

18 PUBLICATION POLICY

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes: specific advance periods for submission and review are specified in the Sponsor's Procedure. The timing of publications (in the event several Centers should be participating in the Study) may be coordinated, and publication delayed if patentable inventions should be involved (for the time required in order to file the relevant patent applications); otherwise, according to the MoH's Decree of May 12, 2006, investigators cannot be precluded from or limited in publishing the results of their studies

(IECs must verify that no excessive restriction is contained in the protocols submitted to their review and approval).

19 STUDY INSURANCE

The Investigator-sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with Section 5.8 of the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the exclusion of those attributable to willful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer's certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.

Based on section 2.4 of the MoH's decree of December 17, 2004, the insurance coverage must be supplied by the hospital or medical research department in case of no profit drug evaluation trial.

20 DURATION OF THE STUDY

The study duration is estimated 88 months (52 for enrollment and 36 for the follow-up).

End of study (Last Patient Last Visit [LPLV]) will be upon completion of the follow up period for the last patient treated in the study. Completion of follow-up for the last patient will occur when the last patient in the study has expired, has been followed for 6 months after their last dose of study treatment, has been lost to follow-up, or has withdrawn consent, whichever occurs first.

21 REFERENCES

1. Groves FD, Linet MS, Travis LB et al. Cancer Surveillance Series: Non-Hodgkin's Lymphoma Incidence by Histologic Subtype in the United States From 1978 Through 1995. J Natl Cancer Inst 2000; 92 (15): 1240-51.
2. Effect of age on the characteristics and clinical behavior of non-Hodgkin's Lymphoma patients. The Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1997; 8 (10): 973-78.
3. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010; 116 (12): 2040-45.
4. Pfreundschuh M, Kuhnt E, Trumper L, et al. Randomized Intergroup trial of first line treatment for young low risk patients (< 61 years) with diffuse large B cell non Hodgkin's lymphoma with a CHOP like regimen with or without the anti-CD20 antibody rituximab: a 6-year follow-up of the Mint study of the Mabthera International Trial (MInT) Group. Proc Am Soc Hematol 2010; abstr 111.
5. Pfreundschuh M, Shubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without Rituximab in elderly patients with aggressive CD20+ B-Cell Lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008; 9 (2): 105-16.
6. Vitolo U, Chiappella A, Angelucci E, et al. Dose-dense and high-dose chemotherapy plus rituximab with autologous stem cell transplantation for primary treatment of diffuse large B-cell lymphoma with a poor prognosis: a phase II multicenter study. Haematologica 2009; 94 (9): 1250-58.
7. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy–sensitive nonHodgkin's lymphoma. N Eng J Med 1005; 333: 1540-45.
8. Guglielmi C, Gomez F, Sebban C, et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the PARMA trial. J Clin Oncol 1998; 16: 3264-3269.
9. Costa LJ, Micallef IN, Inwards DJ, et al. Time to relapse after initial therapy significantly adds to the prognostic valure of the IPI-R in patients with relapsed DLBCL undergoing autologous stem cell transplantation. Bone Marrow Transplant 2008; 41: 715-720.
10. Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B cell lymphoma. Blood 2003; 102 (6): 1989-1996.
11. Lerner RE, Thomas W, DeFor TE, et al. The International prognostic Index assessed at relapse predicts outcomes of autologous transplantation for diffuse large non Hodgkin lymphoma in second complete or partial remission. Biol Blood Marrow Transplant 2007; 13: 486-492.
12. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25 (5): 579-86.

13. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI sponsored International Working Group. J. Clin. Oncol. 1999; 17(4): 1244.
14. Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre and post transplantation positron emission tomography using 18-fluorodeoxyglucose on ppor-prognosis lymphoma patients undergoing autologous stem cell transplantation. Cancer 2007; 10 (6): 1361-1369.
15. Derenzini E, Musuraca G, Fanti S, et al. Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation out come in aggressive B-cell non Hodgkin lymphoma. Cancer 2008; 113: 2496-2503.
16. Terasawa T, Dahaberh IJ, Nihashi T, et al. Fluorine-18-fluorodexyglucose Positron Emission Tomography in response assessment before high dose chemoptehrapy for lymphoma: a systematic review and metanalysis. Oncologist 2010; 15 (7): 750-759.
17. Vellenga E, van Putten WLJ, van't Verr MB, et al. Rituximab improves the treatment of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. Blood 2008: 11 (2): 537-543.
18. Martin A, Conde E, Arnan A, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008; 93 (12): 1829.
19. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010; 28 (27): 4184-90.
20. Wang SY, Racila E, Taylor RP, Weiner GJ. NK-cell activation and antibody-dependet cellular cytotoxicity induced by rituximab-coated target cells is inhibited by the C3b component of complement. Blood 2008; 111(3): 1456-1463.
21. Glennie MJ, French RR, Cragg MS, Taylor RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. Mol Immunol 2007; 44(16): 3823-3837.
22. Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010; 115(22): 4393-4402.
23. Sehn LH, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K, Fowler N, Delwail V, Press O, Salles G, Gribben J, Lennard A, Lugtenburg PJ, Dimier N, Wassner-Fritsch E, Fingerle-Rowson G, Cheson BD. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-93.
24. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase 2 clinical trials. Biometrics 1995;51:1372-1383.
25. Hans CP, Weisenburger DD, Greiner TC Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Hans CP, Weisenburger DD, Greiner TC et al. Blood 2004; 103: 275-282

26. Choi WW, Weisenburger DD, Greiner TC et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin. Cancer Res. 2009; 15: 5494-5502.

27. Olivieri A, Brunori M, Capelli D et al. Salvage therapy with an outpatient DHAP schedule followed by PBSC transplantation in 79 lymphoma patients: an intention to mobilize and transplant analysis. Eur. J. Hematology 2004; 72(1): 10-17

28. Rigacci L, Fabbri A, Puccini B et al. Oxaliplatin-based chemotherapy (desametazone, high dose cytarabine and oxaliplatin) +/- Rituximab is an effective salvage regimen in patients with relapsed r refractory lymphoma. Cancer 2010: 116 (19); Cancer 2010

22 APPENDIXES

Appendix 1: Timing of treatment and investigations

Stage	Baseline	GA101 –DHAP Treatment						ASCT		Follow-Up	
Period		Cy 1			Cy 2	Intermediate response evaluation	Cy 3	Cy 4	Pre-	Post-	Every 3 months for 1st, 2nd year	Every 4-6 months for 3rd year
		Day 1	Day 8	Day 15								
Informed consent	X											
Review Inclusion/Exclusion criteria	X											
Pregnancy test (if applicable)	X											
Serum virology	X											
Ecg/Echo/MUGA	X					X						
Anti-tumor activity	X					X					X[C]	
Clinical examination	X											
Aspirate and bone marrow biopsy	X					X[A]			X[A]	X[A]		
GC/ABC value on diagnostic tissue	X											
PET scan	X					X[B]			X	X		
CT of neck,chest, abdomen and pelvis	X					X			X	X	X[C]	
Adverse events		X			X		X	X				
Hematology	X	X			X	X	X	X	X	X	X	X
Biochemistry	X[D]	X			X	X	X	X[D]	X	X	X	X
Physical examination, complete medical history, ECOG performance status, vital signs	X	X			X	X	X	X	X	X	X	X
Lymph-node or tissue biopsy (centrally pathology review)	X											
Diagnostic Lumbar Puncture	X											
RMN brain/column, endoscopy, ORL visit, etc. according to physician judge and if clinically relevant	X											

[A] : if positive at baseline
[B] : recommended not mandatory
[C] : every 6 months during the first two years after chemotherapy (at month 6-12-18-24)
[D]: is required dosage of serum Ig

Appendix 2: Response Criteria

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Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix 3: NCI Common toxicity criteria

In the present study, adverse events and/or adverse drug reactions will be recorded according to the:

Common Terminology Criteria for Adverse Events (CTCA), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

Appendix 4: Suggested Body Surface Area Calculation

BSA should be determined using the appropriate following calculation:

$$BSA = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

OR

$$BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Appendix 5: Creatinine Clearance Calculation

Creatinine clearance for men and women will be calculated according to the Cockcroft-Gault formula as follows:

In men: $\frac{[(140-age)\times weight(kg)]}{[72\times creatinine(mg/dL)]}$

In women: $\frac{[(140-age)\times weight(kg)]}{[72\times creatinine(mg/dL)]} \times 0.85$

Note: Age (in years), weight (in kg), serum-creatinine (in mg/dL) 72 (normalized to 72 kg body weight and a body surface of 1.72 m^2)

Appendix 6: ECOG performance status scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about □□50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair □□50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 7: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964.

Appendix 8: Study Flow Chart