II. Synopsis

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Global Principal Investigator:	See above
Coordinating Physicians:	Dr. med. Nadine Kutsch Dr. med. Kirsten Fischer
Title of the clinical trial:	A prospective, multicenter, phase-II trial evaluating efficacy and safety of Bendamustine + GA101 (BG) in patients with relapsed CLL followed by maintenance therapy with GA101 for responding patients
Indication:	Physically fit patients with relapsed CLL
Phase:	Phase-II clinical trial

Type of trial, trial design, methodology:	Prospective, multicenter, phase-II trial, open-label
Number of subjects:	Initially, it was planned to enroll approximately 50 eligible patients per treatment arm [FC + GA101 (FCG) and B + GA101 (BG)] (total: ~100 patients). Subsequent sample size adjustment: The FCG group was closed in the course of the study after 9 patients have been randomized to FCG and 9 patients to BG. The recruitment for the BG group will continue in a non-randomized single-arm fashion until 50 patients (e.g. 41 additional patients) have been enrolled. Thus, the total number of patients will be 59 patients.
Rationale:	The type II anti-CD20 antibody GA101 has demonstrated a high efficacy as single agent (ORR 62%) and was well tolerated in previously treated patients with CLL [1]. Additionally, there is evidence that immunochemotherapy consisting of fludarabine, cyclophosphamide and rituximab (FCR) is active in patients with refractory and relapsed CLL [2]. Besides FCR, the combination of bendamustine with rituximab (BR) has shown to be active in both relapsed and previously untreated patients with CLL [3,4]. In preclinical studies GA101, a glycoengineered, humanized type II anti-CD20 antibody, has shown superior activity compared with type I antibodies [5-7]. Therefore, a combination therapy with FC + GA101 (FCG) or B + GA101 (BG) might further improve the therapeutic outcome in relapsed CLL. The CLLR3 trial was designed to investigate and to evaluate and compare the efficacy and safety of induction

with both immunochemotherapies followed additionally by a maintenance therapy with GA101 for responding patients. Recruitment of the FCG group was prematurely closed in the course of the study. Thus, the CLLR3 trial follows the objective to evaluate the efficacy and safety of induction therapy with BG followed additionally by a maintenance therapy with GA101 for responding patients.

Trial objective:

The primary objective of the study is:

- To evaluate the efficacy of Bendamustine plus GA101 (BG) in patients with relapsed CLL.

The secondary objectives are:

- To evaluate the safety of Bendamustine plus GA101 (BG) in patients with relapsed CLL followed by maintenance therapy with GA101 for responding patients.
- To investigate the feasibility of a maintenance therapy with GA101 following Bendamustine plus GA101 (BG) for responding patients.

Study endpoints:

Primary endpoint:

- Best overall response rate (ORR) defined as best response assessed until and including response assessment at follow up 2 (6 months after final restaging/ induction), defined by the proportion of patients having achieved a CR/ CRi, clinical CR/ CRi or nPR/ PR as best response based on the respective population (= number of patients with best response CR/ CRi, clinical CR/ CRi or nPR/ PR

divided by the number of the respective population)

Secondary endpoints:

- MRD levels during treatment and maintenance
- Progression free survival (PFS)
- Event-free survival (EFS)
- Overall survival (OS)
- Overall response to maintenance treatment
- Duration of response in patients with CR/ CRi, clinical CR / clinical CRi or nPR/ PR
- Time to next anti-leukemia treatment
- Overall response rate in biological defined risk groups
- Complete response rate
- Safety parameters during induction and maintenance phase [type, frequency, and severity of adverse events (AEs), AESI (AEs of special interest) and relationship of AEs to study treatment]
- Evaluation of relationship between various baseline markers and clinical outcome parameters
- Evaluation of patients randomized into the prematurely closed FCG study arm with regard to efficacy and safety parameters

Criteria for evaluation: Efficacy:

- Lymph nodes, spleen and liver measurements by physical examination

- Complete blood count (CBC)
- Peripheral blood samples for cytogenetics
- Flow cytometry of peripheral blood for MRD assessment
- Bone marrow aspirate/ biopsy for standard histopathology
- Radiographic staging (including ultrasound, chest X-Ray, CT [if clinically indicated only])
- ECOG Performance Status
- Assessment of constitutional symptoms (for definition please refer to section *5.5 Indications for initiation* of treatment)
- Survival status
- Survey of start and type of next anti-leukemic treatment
- Survey of various subgroup characteristics for example CIRS

Safety:

- Vital signs
- Clinical laboratory evaluations
- Concomitant medications
- AEs by NCI-CTC Version 4

Target Population: Patients must meet the following criteria:

Inclusion Criteria

1. Diagnosis of CLL in need of treatment according to

the iwCLL guidelines [8]

2. Relapsed disease after at least one, but no more than 3 prior regimens for CLL
3. Medically fit patients without relevant comorbidity, defined as total CIRS score ≤6 (single score < 4 for one organ category)
4. ECOG performance status of 0 - 2
5. Hematology values within the following limits unless cytopenia is caused by the underlying disease, i.e. no evidence of additional bone marrow dysfunction (e.g. myelodysplastic syndrome (MDS), hypoplastic bone marrow due to toxicity of prior therapy):
   a. Absolute neutrophil count ≥1.5 x 10^9/L
   b. Platelets ≥50 x 10^9/L and more than 7 days since last transfusion
6. Creatinine clearance >60 ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured after 24 h urine collection
7. Adequate liver function as indicated by a total bilirubin, AST, and ALT ≤2 the institutional ULN value, unless directly attributable to the patient's CLL
8. Negative serological Hepatitis B test (i.e. HBsAg negative and anti-HBc negative, patients positive for anti-HBc may be included if PCR for HBV DNA is negative); negative testing of Hepatitis C RNA; negative HIV test within 6 weeks prior to registration
9. 18 years of age or older
10. Life expectancy >6 months

11. Able and willing to provide written informed consent and to comply with the study protocol procedures

Exclusion criteria

1. Detected del(17p) or *TP53* mutation
2. Refractoriness to FCR / BR
3. Transformation of CLL to aggressive NHL (Richter's transformation)
4. Known central nervous system (CNS) involvement
5. Evidence of significant uncontrolled concomitant disease
6. Major surgery < 30 days before screening
7. Decompensated hemolytic anemia 28 days before screening
8. Hemolytic cystitis 28 days before screening
9. Patients with a history of confirmed PML
10. Prior treatment with GA101
11. History of prior malignancy, except for conditions as listed below (a-d) and if patients have recovered from the acute side effects incurred as a result of previous therapy:
    a. Malignancies treated with curative intent and with no known active disease present for ≥ 2 years before registration
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease at screening
    c. Adequately treated cervical carcinoma in situ

without evidence of disease at screening

d. Surgically adequately treated low grade, early stage localized prostate cancer without evidence of disease at screening

12. Use of investigational agents or concurrent anti-cancer treatment within the last 4 weeks before registration

13. Patients with active infection requiring systemic treatment

14. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies and/ or known hypersensitivity to any constituent of the product

15. Hypersensitivity tofludarabine, cyclophosphamide, bendamustine, GA101 and/ or to any of the excipients for example mannitol

16. An individual organ/ system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive an intensive therapy for CLL

17. Legal incapacity

18. Women who are pregnant or lactating

19. Fertile men or women of childbearing potential unless:

    a. surgically sterile or ≥2 years after the onset of menopause

    b. willing to use a highly effective contraceptive method (Pearl Index <1) such as those listed at section *4.2.2 Exclusion criteria* during study

treatment and for 12 months after end of study treatment

20. Vaccination with a live vaccine within a minimum of 28 days before screening

21. Participation in any other clinical trial which would interfere with the study drug

22. Prisoners or subjects who are institutionalized by regulatory or court order

23. Persons who are in dependence to the sponsor or an investigator

Name of investigational medicinal product (IMP):	Fludarabine, Cyclophosphamide, Bendamustine, Obinutuzumab (GA101)
Study drug supplies:	As non-approved drug for CLL respectively non-approved drugs in this patient population, GA101 will be supplied by Roche and Bendamustine will be provided by Mundipharma during the trial while commercially available preparations of Fludarabine and Cyclophosphamide will be used.
Investigational medicinal product – dosage and method of administration:	Induction: FCG regimen: • GA101 iv infusion: The first dosage of GA101 in cycle 1 may be administered either full dose (1000 mg) on day one if the first infusion of 100 mg is well tolerated by the patient or over two consecutive days (100 mg on first day, remaining 900 mg the following day). •

Cycle 1	Day 1	100 mg

	Day (1 or) 2	900 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycle 2 - 6	Day 1	1000 mg

- Fludarabine iv infusion 25 mg/m2 day 3-5 in cycle 1 or day 2-4 when GA101 is completely dosed on day 1 respectively day 2-4 q4wks, cycle 2 to 6

Cycle 1	Day (2 or) 3	25 mg/m2
	Day (3 or) 4	25 mg/m2
	Day (4 or) 5	25 mg/m2
Cycle 2 - 6	Day 2	25 mg/m2
	Day 3	25 mg/m2
	Day 4	25 mg/m2

- Cyclophosphamide iv infusion 250 mg/m2 day 3-5 in cycle 1 or day 2-4 when GA101 is completely dosed on day 1, respectively day 2-4 q4wks, cycle 2 to 6

Cycle 1	Day (2 or) 3	250 mg/m2
	Day (3 or) 4	250 mg/m2
	Day (4 or) 5	250 mg/m2
Cycle 2 – 6	Day 2	250 mg/m2
	Day 3	250 mg/m2
	Day 4	250 mg/m2

BG regimen:

- GA101 iv infusion:

The first dosage of GA101 in cycle 1 may be administered either full dose (1000 mg) on day one if the first infusion of

100 mg is well tolerated by the patient or over two consecutive days (100 mg on first day, remaining 900 mg the following day).

Cycle 1	Day 1	100 mg
	Day (1 or) 2	900 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycle 2 - 6	Day 1	1000 mg

- Bendamustine iv infusion 70 mg/m² day 3-4 in cycle 1 or day 2-3 when GA101 is completely dosed on day 1, respectively day 2-3 q4wks, cycle 2 to 6

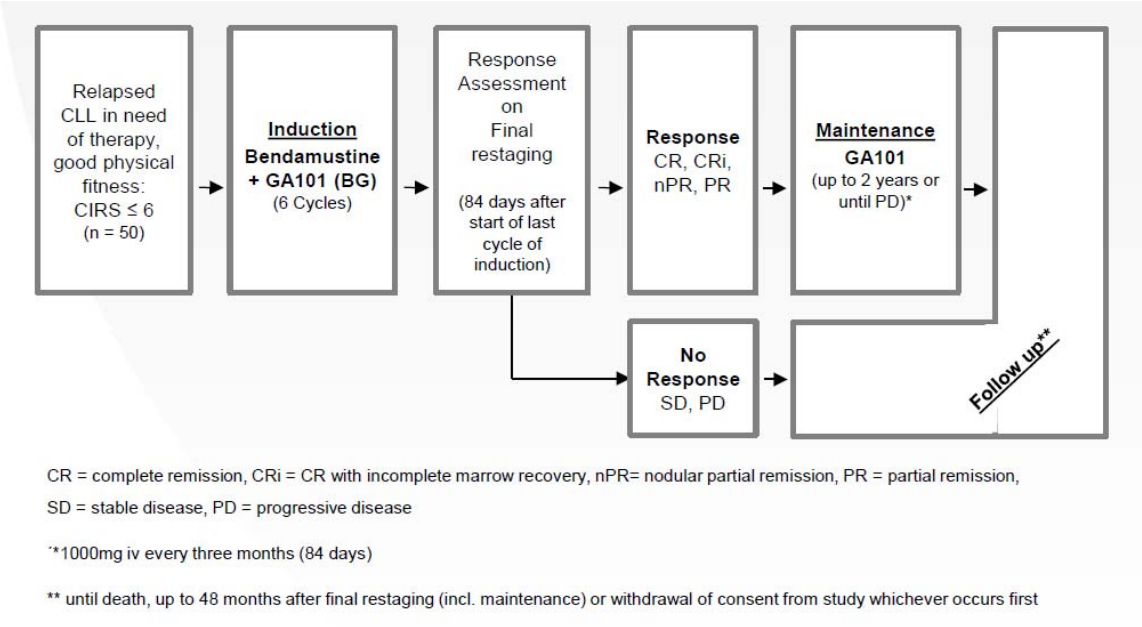
Cycle 1	Day (2 or) 3	70 mg/m²
	Day (3 or) 4	70 mg/m²
Cycle 2 – 6	Day 2	70 mg/m²
	Day 3	70 mg/m²

Maintenance:

After a maximum of 6 cycles of BG or FCG a GA101 maintenance will be initiated for patients in response (CR/ CRi, clinical CR/ CRi or nPR/ PR) at final restaging (84 days after first dose of last cycle of induction administered):

- GA101 1000 mg (flat dose) iv infusion, every 84 days starting on final restaging (84 days after first dose of last cycle of induction administered) and will be continued until progression or if patient does not progress to a maximum of 2 years

Treatment plan:



CR = complete remission, CRi = CR with incomplete marrow recovery, nPR= nodular partial remission, PR = partial remission, SD = stable disease, PD = progressive disease

*1000mg iv every three months (84 days)

** until death, up to 48 months after final restaging (incl. maintenance) or withdrawal of consent from study whichever occurs first

Duration of treatment:

A maximum of 6 cycles of either FCG or BG will be administered; each cycle with a duration of 28 days unless the administration is delayed.

The response to treatment will be assessed after 3 cycles before cycle 4 day 1 (interim staging), 28 days after first dose of last cycle of induction administered (initial response), 84 days after first dose of last cycle of induction administered (final restaging) and henceforth every three months (follow up 1, 2, 3 etc.) until progression and thenceforth every three months for survival and new CLL treatment.

Based on response assessment at final restaging a maintenance therapy with GA101 infusions every three months (84 days) will be initiated for patients in response (CR/ CRi, clinical CR/ CRi or nPR/ PR). The maintenance will be started on final restaging and will be continued until progression or up to a maximum of two years if no progression occurs within that

	time (unless intolerable toxicity does not allow maintenance therapy). Patients will be followed up until death or up to 48 months after final restaging, whichever occurs first. Afterwards the patients are considered end of study. The end of the clinical trial is defined as 60 months after the last patient was enrolled.
Long-term follow up following the end of the study:	To be able to collect long-term follow up data, each subject will additionally before trial recruitment be informed about the importance of long-term follow up data and asked for his/ her consent to the long-term follow up within the GCLLSG registry. For subjects with a written informed consent for the registry trial data for overall survival, secondary malignancies and diseases, further treatments and the course of the disease will be collected. Within the non-intervention GCLLSG registry trial the observation will be continued after the end of the CLLR3 study.
Stopping rules:	Any decision to prematurely terminate the study as a whole will be made by the sponsor in accordance with regulatory and ethical principles. During the study, continual monitoring of efficacy and toxicity will be performed. Criteria for termination of the study as a whole are: • Any new safety concern emerging from this or any other study which would change the current benefit/ risk ratio. This includes that every fatal SAE will be forwarded to the GPI for evaluation of the benefit/ risk ratio. • Any other factor that in the view of the sponsor constitutes an adequate reason for terminating the

study as a whole.

Statistical methods	The analysis of the primary endpoint will be performed on an intention to treat (ITT) - population comprising of all enrolled patients of the BG study arm. In addition, a per-protocol (PP) - population will be defined for a sensitivity analysis of the primary endpoint. This per-protocol population will comprise of all enrolled subjects who are evaluable for response, i.e. who have received at least one dose of any study medication (unless progressed or died before), fulfill the inclusion criteria without any known major protocol violations, and had an evaluable disease assessment at screening and at least one evaluable response assessment post screening. Efficacy of BG is confirmed if the ORR is at least 80% (response rate of an active regimen) and is assessed to be not effective if the ORR is 60% or less (ORR of an uninteresting regimen). The ORR will be estimated using two-sided 95% exact confidence intervals by the Clopper-Pearson method. All 9 patients who have already received FCG until the closure of the recruitment of this study arm will be described separately from the BG study arm with regard to the defined efficacy and safety parameters of the protocol. Analyses will be descriptively only.
Sample size calculation	The primary endpoint (ORR) was used to determine the sample size for the study. Initially, the primary efficacy analysis of

induction treatment with FCG and BG was planned to be performed with a single stage phase II design. The following study assumptions were considered:

The ORR for both arms is assumed to be 60% with corresponding null hypothesis H0: ORR ≤ 60%.

It is expected to improve this rate to 80% for both study arms. The type I error is set to α = 5% and defines the chance that induction with FCG/BG will be investigated further although the true ORR is lower or equal to 60%. The type II error is the chance that an effective treatment will not be studied further. This should not exceed β = 20%, so that it is aimed to achieve a power of (1 - β) = 80%.

According to the above determined study parameters a two-sided one-sample binomial-test with an overall significance level of 5% will have 80% power to detect the stated improvement in ORR from 60% to 80% when the total number of patients in each treatment arm is 42.

To ensure the 42 patients needed, a drop-out rate of approximately 10 - 20% will be assumed. Thus, 50 patients have to be recruited for each study arm (100 patients in total).

In the course of the study it was decided to subsequently adjust the sample size: The recruitment of the FCG study arm was stopped prematurely after 9 patients have been enrolled into the FCG arm and 9 patients into the BG arm.

The recruitment for the BG group will continue in a non-randomized single-arm fashion until 50 patients (e.g. 41 additional patients) have been enrolled.

Sample size calculation was performed with EAST 5 and Binomial tables.

Study duration:	Expected start of recruitment	Q4/2014
	Expected end of recruitment	Q4/2018
	End of the clinical trial	Q4/2023

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GCP conformance: The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.