Universität zu Köln

CLLM1-Protocol of the German CLL-Study Group (GCLLSG)

A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of lenalidomide (Revlimid®) as maintenance therapy for high-risk patients with chronic lymphocytic leukemia following first-line therapy

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I. Synopsis

Title	A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of lenalidomide (Revlimid®) as maintenance therapy for high-risk patients with chronic lymphocytic leukemia following first-line therapy
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Indication	REVLIMID® (lenalidomide) is indicated for maintenance therapy in high risk patients with CLL who responded to first line therapy (MRD+ PR or MRD+ CR)
Definition of high risk	Patients who responded to firstline with MRD levels in the peripheral blood two months after the completion of first line treatment (at final restaging) of either: **a.** $\geq 10^{-2}$ or **b.** $\geq 10^{-4}$ - $<10^{-2}$ combined with at least one of the following factors: • an unmutated IGHV-status • 17p-deletion or • TP53 mutation
Trial design	CLLM1 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that compares the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo maintenance therapy in high-risk subjects with CLL who have achieved at least a partial response (PR) and either: **a.** MRD levels of $\geq 10^{-2}$ or **b.** MRD levels of $\geq 10^{-4}$ - $<10^{-2}$ combined with at least one of the following factors: • an unmutated IGHV-status • 17p-deletion or • TP53 mutation after first line therapy with FCR, FR, BR, Pentostatin-CR or FC (in case of contraindications to receive Rituximab). Initial trial design: For progression free survival (PFS), a 75% improvement from 22.4 months for placebo to 39.2 months on lenalidomide is considered clinically relevant. The PFS distributions are assumed to be exponential with a constant failure rate. When the total number of events is approximately 118 over both treatment arms, then a two-sided log-rank test with an overall significance level of 5% will have 80% power to detect a hazard rate ratio of 0.571. To ensure timely completion of the study, 186 subjects will be needed, providing for a drop-out rate of 7.5%, 200 subjects will be randomized with a 2:1 randomization between the lenalidomide-arm and placebo-arm. Based on the analyses of CLL8 data about 30% of patients after firstline treatment are assessed to be high risk patients. That leads to the number of about 714 patients to be screened.The enrollment rate is estimated at 12.5

	subjects randomized per month, 133 (124+7.5% drop out) subjects in the lenalidomide-arm and 67(62 plus 7.5% drop out) in the placebo-arm. Subsequent adjustment of trial design: In the course of the study it was realized that the recruitment goal of 200 planned patients might not be reached due to significant lower recruitment rates as planned. Thus, it would not be possible to perform the planned final analysis after 118 PFS events, so that the study would not be analyzable at the end of recruitment. Therefore, it was decided to subsequently revise the initial design according to a group sequential design including two interim analyses and one final analysis. The first interim analysis was performed on a dataset with data cut-off date 31st March 2016. At this time point 89 patients have been randomized into the study and further randomization was closed. The results of the first interim analysis were statistically significant, robust and reliable with regard to the pre-specified stopping boundaries given by the Hwang-Shih-DeCani spending function (with parameter $\gamma = -2$ for the lower futility boundary parameter $\gamma = -4$ for the upper efficacy boundary). Based on these results, based on the recommendations of DSMB, it was decided to unblind the patients and to further observe the patients in the placebo arm and to continue with the treatment in the lenalidomide arm. The further observation of the subjects in the study is with the objective to collect further safety data and data for the secondary endpoints including overall survival.
Objectives	Primary Objective: • To compare the efficacy of lenalidomide versus placebo maintenance therapy. The primary efficacy objective of this study is to investigate if lenalidomide maintenance therapy is superior to placebo maintenance therapy in prolonging PFS, for subjects with a high risk of early progression following first-line treatment. All subjects, including both subjects who do and do not achieve MRD negativity will be treated up to disease progression with maintenance therapy. Secondary Objective: • To evaluate the prolongation of overall survival (OS) of lenalidomide versus placebo maintenance therapy • To evaluate the safety of lenalidomide versus placebo maintenance therapy.
Endpoints	Primary Endpoint: • Progression-Free Survival (PFS) based on independent review committee Secondary Endpoints: • Progression-Free Survival (PFS) based on investigator's assessment • Progression-free survival based on investigator's assessment censoring subjects who started new anti-leukemic therapy before disease progression • Overall Survival (OS) • Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide or placebo], premature withdrawals • MRD levels per central lab (Evaluation by flow cytometry and comparison of MRD levels immediately after the completion of first line therapy to levels 6,12, 18 and 24 months and subsequently annually during

	treatment with lenalidomide or placebo, respectively). It is anticipated that some subjects who are randomized to the lenalidomide arm, will further decrease MRD levels over the duration of treatment in contrast to the subjects randomized into the placebo arm • Health-Related Quality of Life by EORTC QLQ C30 and EQ-5D • Time to next treatment • Event-free survival • treatment free survival after 2ndline treatment Exploratory: • Cytogenetic fluorescence in situ hybridization (FISH), Biomarker analyses (Zeta-chain-associated protein kinase 70 [ZAP 70], CD38, IGHV mutational status, and immune cell analyses (NK and T cells) • Thymidine kinase, Beta-2 Microglobulin (β2M) • Genetic or biological markers of predictive value
Assessments	Efficacy: • Lymph nodes, spleen and liver measurements by physical examination • Complete blood count (CBC) • Peripheral blood smear • Flow cytometry of peripheral blood for MRD assessment • Bone marrow aspirate/biopsy for standard histopathology and flow cytometry for MRD assessment • Computed tomography (CT) scans if clinically indicated • ECOG Performance Status • Assessment of constitutional symptoms Safety: • Vital signs • Clinical laboratory evaluations • Pregnancy testing for female subjects with childbearing potential • Electrocardiogram (ECG) • Concomitant medications • AEs by NCI CTCAE Version 4.0 • Second Primary Malignancy. Subjects will be contacted 4 times per year during the survival follow up until the end of the study for observation for second primary malignancy. • HRQL will be measured by EORTC QLQ C30 and EQ-5D Exploratory: • FISH analyses, ZAP 70, CD38, IGHV mutational status assessment, quantitative immunoglobulins assessment and flow cytometry (MRD)

	• Thymidine kinase, Beta-2 Microglobulin (β2M) • Genetic or biological markers of predictive response • NK and T cell analyses Health Economics: The EORTC QLQ-C30 and the EQ 5D will be administered as a measure of health-related quality of life. For detailed explanation see section Health Economics 4.11.1.5
Number of subjects	Initial sample size: 200 (186 plus 7.5% drop out rate) subjects will be enrolled and randomized (2:1) into two arms: lenalidomide daily or placebo daily until disease progression. Based on the analyses of CLL8 data about 30% of patients after firstline treatment are assessed to be high risk patients. That leads to the number of about 714 patients to be screened..Randomization has been closed in March 2016. 89 patients had been randomised for the study.
Key inclusion criteria	1. Must understand and voluntarily sign an informed consent form. 2. Age ≥ 18 years at the time of signing the informed consent form. 3. Must be able to adhere to the study visit schedule and other protocol requirements. 4. Must have a documented diagnosis of CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia[1]). 5. Must have been treated with one of the first line induction therapies: fludarabine/cyclophosphamide/rituximab, or bendamustine/rituximab or fludarabine/rituximab or pentostatin/cyclophosphamid/rituximab or fludarabine/cyclophosphamide, (in case of hypersensitivity reactions to Rituximab). 6. Must have achieved a response of at least PR (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia[1]) following completion (minimum 4 cycles) of first-line induction therapy prior to randomization (documentation of response status must be available) and have either: a. MRD levels in the peripheral blood at final restaging of $\geq 10^{-2}$ or b. MRD levels in the peripheral blood $\geq 10^{-4}$ - $<10^{-2}$ combined with at least one of the following factors: - unmutated IGHV-status - 17p-deletion - TP53 mutation 7. Must have completed last cycle of at least 4 cycles of first-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization. 8. Subjects who completed first line induction treatment with less than 6 but at least 4 cycles should document reason for early discontinuation 9. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2. 10. Negative serological Hepatitis B test or negative PCR in case of positive serological test without evidence of an active infection, negative testing of Hepatitis C RNA, negative HIV test within 6 weeks prior to randomization. 11. Females of childbearing potential (FCBP)† must: a. Have two negative medically supervised pregnancy tests prior

† Definition: This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

	to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices complete and continued sexual abstinence. b. Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, two reliable forms of effective contraception simultaneously to achieve a PEARL-Index <1 without interruption (Highly effective methods: Intrauterine device (IUD), Hormonal (birth control pills, injections, implants), Tubal ligation, Partner's vasectomy, Additional effective methods: Male condom, Diaphragm, Cervical Cap), 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy. 12. Male subjects must: a. Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy. b. Agree to not donate semen during study drug therapy and for a period after end of study drug therapy. 13. All subjects must: a. Have an understanding that the study drug could have a potential teratogenic risk. b. Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy. c. Agree not to share study medication with another person. d. Be counseled about pregnancy precautions and risks of fetal exposure. 14. Willingness to inform the general practicioner
Key Exclusion Criteria	1. A CIRS Score of more than 6 or a single score of 4 for an organ system limiting the ability to receive an intensive therapy for CLL. 2. Active infections requiring systemic antibiotics. 3. Systemic infection CTC grade 3 or 4 that has not resolved > 2 months prior to randomization in spite of adequate anti-infective therapy. 4. Autologous or allogeneic bone marrow transplant as first line therapy. 5. Pregnant or lactating females. 6. Systemic treatment for CLL in the interval between completing the last cycle of first-line induction therapy and randomization. 7. Participation in any clinical study or having taken any investigational therapy which would interfere with the study drug for a disease other than CLL within 28 days prior to initiating maintenance therapy. 8. Known presence of alcohol and/or drug abuse. 9. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization. 10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following: a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Carcinoma in situ of the cervix d. Carcinoma in situ of the breast e. Incidental histological finding of prostate cancer (TNM stage of T1a or T1b) 11. History of renal failure requiring dialysis. 12. Prior therapy with lenalidomide.

	13. Any of the following laboratory abnormalities: 14. Calculated (method of Cockroft-Gault) creatinine clearance of <60 mL/min 15. Absolute neutrophil count (ANC) < 1,000/µL (1.0 X 10^9/L) 16. Platelet count < 50,000/µL (50 X 10^9/L) 17. Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN) 18. Serum total bilirubin > 2.0 mg/dL (with the exception of Gilbert's Syndrome) 19. Uncontrolled hyperthyroidism or hypothyroidism. 20. Venous thromboembolism within one year. 21. ≥ Grade-2 neuropathy. 22. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia. 23. Disease transformation (active) (i.e. Richter's Syndrome, prolymphocytic leukemia). 24. Known allergy to allopurinol, if the subject has bulky disease 25. Prisoners or subjects who are institutionalized by regulatory or court order or persons who are in dependence to the sponsor or an investigator.
Study duration	• start of recruitment: 07/2012 • end of recruitment (randomization phase): 03/2016 Recruitment duration: Approximately 45 months Subjects will receive study drug until disease progression, unacceptable toxicity or voluntary treatment withdrawal, whichever occurs first. Follow-up for disease progression up to 60 months after randomization of last patient (or subject died/became lost to follow up before the 5 years). Total study duration will be approximately 102 months (January 2021).
End of study	End of study: about 60 months after randomization of last subject, approximately in January 2021.
Screening	Patients are eligible with a confirmed CLL according to the iwCLL-guidelines and after they responded (PR or CR) to 6 courses (in case of toxicities at least 4 courses) of treatment with immunochemotherapy with FCR, BR, FR, PCR or FC. Registration should take place after the completion of first-line treatment and response assessment. The registration form and the screening pages 1-16 (marked with "PRE" and "SCREENING" of the CRFs) should be faxed to the GCLLSG Central Study Office. Screening should start after the completion of the last cycle of the firstline treatment. Subjects will sign informed consent prior to undergoing any study-related procedures. Not earlier than 56 days after day 28 of the last cycle of firstline treatment the following sample is to be taken and to be sent to the central lab in Kiel: • blood samples for the analysis of MRD levels Further screening assessments for protocol eligibility should be performed within 28 days prior to randomization. Subjects who did not respond to first line treatment or who develop PD during screening will not be eligible for this study. A peripheral blood sample for direct antiglobulin test (DAT) should be collected during screening and analyzed at the local laboratory. During screening, CT scans of the neck, chest, abdomen and pelvis will also be performed for all subjects; in particular, they will be used to document the status (PR or CR) of subjects entering the study. CT scans might be repeated if

	clinically indicated after approximately 12 cycles and progression of disease at the discretion of the inveatigator. If, during the screening period, the subject has a correctable event that prevents randomization and the event cannot be corrected within the 28 day screening period, the subject may be re-screened; however, the CT scans and bone marrow aspirate and biopsy will not need to be repeated if those tests were implemented within 56 days prior to randomization and the subject's clinical status remains the same. If clinicaly indicated, following sample is to be taken between screening and randomization and to be sent to the central lab in Kiel: • both bone marrow aspirate and bone marrow biopsy (for both, confirmation of response and MRD level) Subjects with MRD levels of $\geq 10^{-2}$ are eligible, even if results for the other risk parameters are missing, subjects with MRD levels of $\geq 10^{-4}$ but $<10^{-2}$ are eligible if they can be stratified: Results of local/ central labs for the required tests (Immunophenotyping, and results for at least either FISH, or TP53 or IGHV) should be available. For subjects with MRD levels of $\geq 10^{-4}$ but $<10^{-2}$ but with missing results for IGHV, investigators will be encouraged to draw a blood sample and to ship the sample for analysis to the central lab in Ulm. MRD status after firstline treatment can only be assessed within the central lab in Kiel. For all subjects who underwent pre-screening procedures before the activation of amendment 3, results of central lab samples will be used.
Repeated samples for central labs	MRD status will be assessed by peripheral blood flow cytometry for the screening of the study and will be repeated for all subjects still in remission after 6 cycles, 12 cycles, 18 cycles, 24 cycles of treatment and then annually. Immediately after confirmation of randomization, MRD assessment will also be performed in the bone marrow for all subjects who achieved a response to first line treatment and proceed with the screening process. Bone marrow biopsy and aspirate should be sent to the central lab in Kiel where the histopathological assessment and the MRD analysis will be done and from where the trephine biopsies will be forwarded to the Section of Hematopathology of the University Hospital of Schleswig-Holstein, Campus Kiel. FISH will be repeated at the time point of progression, if progression occurs during the conduct of the study.
Randomization	Randomization must occur no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) from the completion of the first-line induction therapy received by the subject in order for the subject to be eligible for enrollment into this study. Subjects meeting all eligibility criteria will be randomized (2:1) in a double-blind manner to receive maintenance therapy with either lenalidomide or placebo up to disease progression. The randomization procedure will be accomplished by a validated interactive voice response system (IVRS) and/or an Interactive Web Response System (IWRS). Subjects will be stratified at randomization by MRD level ($\geq 10^{-2}$ vs. $< 10^{-2}$ and $\geq 10^{-4}$).
Blinding	For this trial, study subjects, investigators, staff, and the sponsor's clinical and medical representatives will all be blinded to the treatment assignments. Both study medication and placebo capsules are identical in appearance. Randomization, drug dispensing, dose reduction/escalation, and drug discontinuation will be accomplished by an IVR/IWR system. Authorized site personnel must contact the IVRS/IWRS for screening, randomization, study drug assignment at the beginning of each cycle, to register dose reductions or escalations, and treatment discontinuation. Confirmation of each call will be sent to the investigational site and the Central Office oft he German CLL Study

	Group.
Unblinding	History: The third protocol amendment, dated 20th October 2015, allowed for the introduction of up to two interim analyses. Each interim analysis would allow early stopping for either efficacy or futility (non-binding) if pre-specified boundaries were crossed. On 17th June 2016, the DSMB met to discuss the results of the first interim analysis. The DSMB concluded the stopping boundary for efficacy has been surpassed and, as such, recommended that the subjects be unblinded. On 24th June 2016, the Global Principal investigator, PD DR. Barbara Eichhorst, agreed with conclusion and recommendation of the first interim analysis by the DSMB leading to the fourth amemendment of the protocol. After approval of fourth amendment the patients will be centrally unblinded, sites will be notified about the unblinding with a written confirmation. All patients will be further observed. Patients of the lenalidomide arm will continue with the treatment After the unblinding process a new drug supply system will be implemented with unblinded study medication.
Investigational product and study drug supplies	Lenalidomide will be supplied in 2.5mg, 5mg, 10mg, 15mg, 20mg and 25mg capsules. Study drug will be packaged in blister cards containing 84 study capsules for 28 days. Patients in the lenalidomide arm will receive 3 capsules per day, one capsule with the assigned dose level of lenalidomide and two capsules with placebo. Subjects assigned to active treatment will receive 28 days of active drug (with the exception of those subjects de-escalated to the 2.5 mg every other day dose level). Those subjects de-escalated to lenalidomide 2.5 mg every other day will receive 14 days of active drug and 14 days of placebo. Allopurinol –only for those subjects entering the study with bulky disease- will be supplied as 300 mg tablets for oral administration labeled as investigational product. The drug supply chain will be changed to a drug order system with unblinded labelled study medication. Once the sytem is active, patients will receive Lenalidomide 28ct bottles for 2.5mg, 5mg, 10mg, 15mg, 20mg & 25mg strengths. White clinical capsules, provided in white HDPE child resistant bottles will be used.
Study drug administration	Treatment schedule: lenalidomide daily starting with 5 mg daily on days 1-28 of the first 28-day cycle. If the 5 mg dose level is well tolerated, escalation to 10 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second and up to the sixth cycle; further escalations starting with the 7^{th} cycle and up to the 12^{th} cycle to 15 mg daily is permitted. If after 12 cycles of treatment subjects still present with MRD levels of ≥ 10^{-4} in peripheral blood and previous dose levels are well tolerated, starting with the 13^{th} cycle up to progression 20 mg daily is permitted. If after 18 cycles of treatment for subjects still present with MRD levels of ≥ 10^{-4} in peripheral blood and previous dose levels are well tolerated, starting with the 19^{th} cycle up to progression 25 mg daily is permitted. 25 mg is the maximal daily dose of lenalidomide.
Concomitant medication	Premedication: • Allopurinol should be given to subjects assigned to the lenalidomide-arm who are assessed as having bulky disease i.e. show at least one lymph node of more than 5 cm in the largest diameter following completion of first-line induction therapy.

	Prophylaxis: • Antimycotic and antibiotic prophylaxis if clinically indicated • For prophylaxis of thromboembolic events please see 4.10.7. The investigator may use appropriate anti-coagulation prophylactic therapies (i.e. LMW heparin, fondaparinux, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (i.e. subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history). Subjects with no history of DVT or arterial thromboembolic events within the past 12 months, no clear indication or contraindication for antiplatelet or anticoagulant therapy, with no active bleeding, and who are not considered to be at high risk of bleeding should receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug. • NSAIDs, corticosteroids, narcotic analgesics in case of tumor flare syndrome (TFS) • Prophylaxis for TLS, thromboembolism and infection, and treatment of tumor flare reaction (TFR) Other therapies considered necessary for the subject's well being may be administered at the discretion of the Investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications as well as growth factors and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with chroniclymphocytic leukemia or its therapy.
Exploratory Endpoints	To identify if there are biomarkers predictive of response to lenalidomide in CLL subjects, samples will be collected at study entry (only for patients who underwent pre-screening procedures before activation of amendment 3) and at progressive disease or discontinuation of treatment. Whole blood will be collected and both plasma and peripheral blood mononuclear cells (PBMC) will be prepared. Plasma and PBMC will be used for analysis of protein markers. PBMC will also be used for DNA and RNA isolation for the analysis of genetic markers. Markers of high risk disease such as chromosomal abnormalities by FISH and ZAP70, and IGHV mutational status are routinely used for the classification of CLL subjects. This exploratory analysis will complement these markers by identifying additional genome-wide genetic aberrations such as gene mutations or copy number variation. Such studies have yielded insight into the molecular complexity of CLL[2] and may help to identify molecular subgroups of subjects that are responsive to lenalidomide. mRNA analysis can also be used to identify or confirm molecular markers of response. Protein levels can then be quantitated to confirm alteration in pathway activation or assess specific proteins that may affect response to lenalidomide. In order to get insights into subpopulation dynamics during therapy, expression levels of proteins with impact on cell survival and homing will be compared between the diagnostic sample and residual cells after therapy as well as during maintenance and placebo treatment, respectively. Additional exploratory analyses may be conducted. T- and NK-cell analyses will be done in order to investigate the composition of T- and NK cell subpopulations after induction therapy, the changes induced into T- and NK cell subpopulations induced by lenalidomide maintenance vs. in the placebo arm. T- and NK cell subpopulation composition and changes will be related to PFS, response, MRD kinetics and toxicity of the drug
Statistical methods	**Populations**: The primary analysis population for efficacy is the intent–to-treat population

defined as all subjects being randomized. Subjects will be assigned to treatment groups as randomized. In addition, a per-protocol population (PPS per protocol set) will be defined for a sensitivity analysis of PFS. This per-protocol population will comprise all subjects who have completed study therapy (defined as having received at least two complete cycles of study therapy) unless progressed or died before, provided they fulfill the inclusion criteria and have no major protocol violations (see listing below). Subjects are assigned to treatment groups as treated. The purpose of the per-protocol analysis is to assess the robustness of the primary analysis (based on the intent-to-treat population) and to quantify more precisely the magnitude of the potential clinical benefit of the treatment in the target population.

Subjects showing any of the protocol violations listed below will be excluded from the per protocol analysis:

- unconfirmed diagnosis of CLL by IWCLL criteria
- less than 2 cycles of randomized treatment (except for early progression or death)
- inadequate tumor assessment at screening
- no screening assessments of lymphocyte count
- previous treatment of CLL by chemo-, radio- or immunotherapy other than the first-line therapy specified by the protocol

All safety parameters will be analyzed on the safety population. This population includes all subjects who have received at least one dose of trial treatment, whether withdrawn prematurely or not. The safety parameters will be presented according to the therapy the subject received.

Primary analysis of the primary endpoint:

This analysis will be performed on the ITT-population.

The primary objective of the study is to compare the following hypothesis:

Progression free survival (PFS) of Lenalidomide versus Placebo i.e.

H0: Lenalidomide = Placebo versus H1: Lenalidomide ≠ Placebo

The two treatment arms will be compared for PFS based on the assessment of an independent review committee by using a two-sided non-stratified log-rank test. In addition Kaplan-Meier estimates, median time of progression-free survival as well as progression-free survival rates for one, two and three years after randomization with 95% confidence intervals will be reported.

Two formal interim analyses have been subsequently planned when 20% (24 events) and 41% (48 events) of the total 118 PFS events have been observed. PFS will be tested at the significance level determined using the Hwang-Shih-DeCani spending function with parameter $\gamma = -2$ for the lower futility boundary and the Hwang-Shih-DeCani spending function with parameter $\gamma = -4$ for the upper efficacy boundary. The significance level will be adjusted to incorporate the α-spent at the interim analyses, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

Based on the results of the first interim analysis results, the DSMB concluded that the stopping boundary for efficacy has been surpassed and, as such, recommended that the subjects should be unblinded. All patients should be further observed and patients in the lenalidomide arm should continue with the treatment. The further observation of the subjects in the study has the objective to collect further safety data and data for the secondary endpoints.

Concerning future analyses, the second interim analysis will be omitted and the final analysis will be conducted either as soon as all patients have experienced disease progression or at the end of the study (30 days after end of treatment of

	the last subject, estimated latest in March 2021). The final analysis will be performed in an unblinded fashion by the statistician of the GCLLSG.A two-sided stratified log-rank test of PFS based on the investigator's assessment with the MRD level as stratification factor will be performed on the ITT-population to confirm the primary statistical analysis. With regard to sensitivity of the primary statistical analysis, a two-sided non-stratified log-rank test of PFS based on the investigator's assessment will be performed on the per protocol population. Other time to event endpoints will be analyzed in a similar way as the primary analysis on the ITT-population. Rates will be compared using a chi-square test or exact-test of Fischer, as appropriate. Rates and 95% confidence limits will be given for each treatment group. The effect of prognostic factors will be assessed in exploratory multivariate analyses. Summary descriptive statistics will be performed for continuous variables.
Randomization procedures:	Randomization will be accomplished by an IVRS/IWRS to ensure timely registration and randomization. Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to call into the IVRS/IWRS to enroll subjects. The system will present a menu of questions by which the research personnel will identify the subject and confirm eligibility. When all questions have been answered, including questions regarding the results of pregnancy tests for FCBP, the IVRS/IWRS will assign a subject number and study drug to the eligible subject. IVRS/IWRS will fax a confirmation of registration and drug assignment for each subject to the site and the study office of the GCLLSG. Subjects will be randomized (2:1) to receive lenalidomide or placebo. Randomization procedures are completed as of 31st March 2016..
GCP conformance:	This study will be conducted in accordance with good clinical practices as described in the ICH E6 Guideline for Good Clinical Practice, adopted 1 May 1996. The guideline may be obtained at URL: http://www.fda.gov/cder/guidance/959fnl.pdf or URL: http://www.ich.org. Furthermore the study will be performed in compliance with the EU Directive on clinical trials 2005/028/EC. In Germany, the requirements according to the following documents will be fulfilled: Deutsches Arzneimittelgesetz (Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 19.10.2012 BGBl I S. 2192 in Kraft getreten am 26.10. 2012) and "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen" from August 9th. 2004. The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The Sponsor will be responsible for preparing documents for submission to the relevant EC as well as the Clinical Trial Application to the relevant regulatory authorities and obtaining written approval of both the EC and the regulatory authorities for this study. The approval will be obtained prior to the initiation of the study.
Financing:	Study will be supported by CELGENE International Sàrl, Route de Perreux 1, 2017 Boudry, Switzerland
Follow up	During the maintenance treatment subjects will be followed every cycle (approximately 4 weeks) for safety. Staging procedures to assess the status of the disease will be done after 3 cycles (approximately every 12 weeks). Subjects who discontinue study medication without experiencing progressive disease will be followed every 3 months until progressive disease occurs. After progression subjects will be followed every 3 months for survival and second

	primary malignancies up to the end of the study.
Long term follow up for survival and late toxicities following the end of the study	CLLM1 trial will end after 102 months duration. To be able to collect long term follow up data, each subject will additionally 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 planned GCLLSG registry trial. For subjects with a written informed consent for the registry trial data for overall survival, late toxicities such as secondary malignancies, further treatments and the course of the disease will be collected. Within the non-interventive GCLLSG registry trial the observation will be continued after end of the CLLM1 study in 2021 since the primary end-point in the CLLM1 study is progression-free survival (PFS). However, the overall survival is a clinically important secondary endpoint in CLLM1. The outcome after progression is critical an d responses to second and subsequent therapies may differ between the trial arms. Therefore it is essential to report both overall survival and PFS. In addition, late toxicities, such as MDS or AML, EBV-associated lymphoproliferative disease or Hodgkin`s disease, late opportunistic infections and second primary malignancies, are increasingly seen and are likely to differ depending on the intensity of therapy. Moreover, meta-analysis of several phase 3 trials with long follow-periods is desirable. The sponsor has ongoing responsibility for safety reporting for their trials and for any late safety aspects. In addition unless the trials have long-term follow-up any late beneficial effects of the therapies will be lost.

II. Table of contents

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III. Abbreviations

abbreviation	Meaning
ADH	Antidiuretic hormone
ADL	Activities of Daily Living
AE	Adverse Event
AIHA	autoimmune hemolytic anemia
AIP	autoimmune phenomena
ALC	Absolute lymphocyte count
Allo-SCT	Allogeneic stem cell transplant
ALT (SGPT)	Alanine aminotransferase
AML	acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BR	Bendamustine, Rituximab
BSA	body surface area
CALGB	Cancer and Leukemia Group B
CBC	Complete Blood count
CD	cluster of differentiation
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CR	Complete response/remission
CRF	Case Report Form(s)
CRi	complete remission with incomplete bone marrow recovery
CT scan	Computerised tomography scan
CTC	Common Toxicity Criteria
CXR	Chest Xray
DFS	Disease free survival
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram
EFS	Event Free Survival
eod	every other day
EORTC-QLC30	European Organization for the Research and Treatment of Cancer Quality of Life questionnaire (c30)
FC	Fludarabine and cyclophosphamide
FCBP	Female of Childbearing Potential
FCR	Fludarabine, Cyclophosphamide, Rituximab
FISH	Fluorescent in situ hybridization
GCLLSG	German CLL Study group
G-CSF	Granulocyte colony stimulating factor
Hb	Hemoglobin
HBV	Hepatitis B virus
HCT	hematocrit
HIV	Human Immunodeficiency Virus
i.v.	Intravenous
ICH	International Conference on Harmonization

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMSE	Institute for Medical Statistics and Epidemiology
IRR	Infusion related reaction
ITP	idiopathic thrombocytopenia purpura
ITT	Intent to treat
IUD	Intra Uterine Device
LDH	Lactate dehydrogenase
LKP (GPI)	Global Principal Investigator (Leiter der klinischen Prüfung)
MCV	Mean corpuscular volume
MDS	myelodysplastic syndrom
MRD	Minimal residual Disease
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
nPR	Nodular partial response/remission
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PEI	Paul-Ehrlich-Institut
PFS	Progression Free Survival
PJP	pneumocystis jiroveci-pneumonia
PLL	Prolymphocytic leukemia
p.o.	Per os: Orally
PR	Partial response/remission
PS	Performance status
RNA	Ribonucleid acid
SAE	Serious Adverse Event
SD	Stable disease
SLL	Small Lymphocytic Lymphoma
SNP	Single nucleotide polymorphisms
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLS	Tumor lysis syndrome
TTNT	Time to new CLL treatment
TTP	Time to progression
ULN	Upper limit of normal
WBC	White Blood Count
WHO	World's Health Organization

1. Introduction

Chronic lymphocytic leukemia is the most common adult lymphoid malignant disease in western countries, affecting about five in 100,000 of the population per year.[3,4] Pathogenetically and cytomorphologically CLL belongs to the group of low-grade non-Hodgkin's lymphomas. Its clinical course is highly variable, survival after diagnosis can range from months to decades, and can be predicted by use of various criteria[5]. Extent of disease at diagnosis is a major determinant of final outcome and is mainly reflected by enlargement of lymph nodes, liver and spleen, as well as the degree of impairment of normal hematopoiesis. These criteria can be used to define different stages of the disease that are related to prognosis and provide the basis for therapeutic decisions[6,7]. Chromosomal abnormalities[8], or mutations of the immunoglobulin heavy variable chain (IGHV) gene[9,10] predict the course of the disease. The cause of CLL is not known. Additional adverse prognostic factors, such as high serum titers of ß2-Microglobulin, thymidine kinase[11,12] ZAP70 and CD 38 expression[13,14] have been discovered.

The past decade has produced rapid progress in the management of chronic lymphocytic leukemia. The addition of monoclonal antibodies to the combination of purine analogues with alkylating drugs, particularly fludarabine and cyclophosphamide improved the rates of clinical response, complete remission, and progression-free survival (PFS).[15-22] Fludarabine, bendamustine and monoclonal antibodies, alemtuzumab, rituximab and ofatumumab, have been approved by the European and/or American regulatory agencies.

Results of the CLL8 trial of the GCLLSG have shown that a high percentage of complete remissions (44%), long lasting progression free survival (PFS; median PFS of 51.8 months) and a benefit for the overall survival with a reduced risk for death of 33% (p=0.01) when compared to FC can be achieved with fludarabine, cyclophosphamide and rituximab (FCR) in first line therapy of CLL.[20] Besides FCR, combinations on the backbone of bendamustine, a hybrid alkylating agent with properties of a purine-analogue, seem to be very active in CLL.[22-25] However, in spite of the improvements achieved, there are subjects with a poor response to intensive first line therapy (e.g. FCR or FCR-like regimen); these subjects are disadvantaged in terms of overall survival (OS) and should be considered as subjects with ultra high risk-CLL.[26]

Subgroup analyses in the CLL8[27] trial revealed that subjects with a median progression free survival (PFS) of < 24 months after randomization showed a significantly shorter overall survival (OS) compared with subjects achieving a PFS of ≥ 24 months. 15 % of these subjects were characterized by both, the presence of 17p deletions and TP53 gene mutations, another 7.5% by TP53 mutation alone. Interestingly, the majority of subjects with a poor prognosis could not be defined by a mutation of TP53 or del(17p). An analysis showed that a combination of minimal residual disease (MRD) levels of $\geq 10^{-2}$ or a combination of MRD levels of $\geq 10^{-4}$ to $< 10^{-2}$ plus at least one of the three parameters (del(17p) or TP53 mutation or an unmutated IGHV-status) defined a group of subjects at high risk of early progression (HR). The median PFS of HR subjects was 22 months, the median PFS for subjects defined as low risk (LR; n=103) was 69 months. HR subjects had a 6.4 fold increased risk for progression (HR 6.4, 95% CI: 3.970-10.347; p<0.0001) and a 5.7 fold increased risk for death, with a median OS of only 57 months (assessed from the beginning of FCR therapy). In contrast, median OS was not reached in the LR group at the time point of the analyses (HR 5.758, 95% CI: 2.799-11.844, p<0.0001). The combined use of genetic markers and an MRD assessment two months after the completion of first line treatment

(final restaging) allows the identification of CLL subjects with a very poor prognosis after FCR therapy. The high risk group identified by this approach should be treated within clinical trials using novel strategies including maintenance protocols[28].

The prognostic relevance of the quality and duration of response to a previous treatment is apparent. Analyses of different trials evaluating various therapeutic options demonstrated that the response to treatment, in particular the achievement of a complete remission or nodular partial remission according to the IWCLL guidelines[1] has an impact on the duration of time to treatment failure, as well as PFS and overall survival[17,18,29]. Furthermore, response to treatment was shown to be an independent prognostic factor for survival in a large trial conducted by Catovsky et al.[30] Tam et al.[18] demonstrated that treatment might alter the natural history of CLL because the response to treatment was shown to counterbalance the impact of pretreatment prognostic factors; in subjects who achieved a complete response, the duration of remission was similar for subjects with and without adverse prognostic factors. This assumption is in concordance with the finding of two analyses demonstrating that chemo immunotherapy, in particular treatment with FCR, might overcome the adverse prognostic impact of a del(11q) chromosomal aberration[20,31]. Moreover, achievement of a complete response or a minimal residual disease (MRD)-negative remission improves the time to progression or overall survival[32,33]. As a failure to respond to therapy or a short remission duration of only 1 or 2 years are associated with a dismal prognosis,[26] these situations demand a change in treatment strategy to more aggressive therapeutic options in physically fit subjects (as defined by CIRS score). MRD can be detected by standardized methods such as multicolor flow cytometry and real-time quantitative PCR in peripheral blood and bone marrow[34]. The cut-off level is currently arbitrarily defined as one CLL cell per 10,000 leukocytes; subjects are defined as MRD negative if their disease burden is below this threshold[35]. The MRD detection by flow cytometry is equally sensitive for peripheral blood and bone marrow samples, except for subjects treated with alemtuzumab, rituximab or other antibodies targeting CLL cells. In these cases, a bone marrow sample is needed following the first 3 month of therapy[35]. The MRD level achieved by various therapies predicts the duration of PFS and treatment-free survival, as well as overall survival[33,36-40] and is an independent prognostic factor irrespective of type or line of therapy[33]. Therefore, the achievement of an MRD-negative remission might become a new primary treatment goal and could guide future treatment decisions. In addition, because MRD assessment is a powerful tool to assess early treatment response,[33] it will facilitate the development of novel agents in CLL. Prospective clinical trials evaluating the benefit from additional treatments intending to eradicate MRD are needed[1].

The assessment of MRD has become a very important endpoint with prognostic impact in clinical trials[33]. Very recently the GCLLSG established the independent prognostic significance of MRD in a cohort of 493 subjects from the CLL8 trial. MRD levels below 10^{-4} were correlated with longer PFS. In that investigation, progressively higher MRD levels, even within the range of MRD positivity, predicted for increasingly shorter PFS and OS, thus corroborating earlier results from a much smaller cohort [38]. Moreover, MRD levels predicted PFS and OS independently from all other established risk factors in this disease when assessed in multivariate Cox regression models. The prognostic significance of MRD levels could be demonstrated in both subjects who achieved a clinical CR and PR. Most importantly, PFS was similar in both treatment arms of the CLL8 trial once subjects were grouped according to the MRD levels achieved after therapy. Based on this data, MRD quantification in CLL qualifies as a parameter to compare treatment efficacy between the arms of randomized trials prior to the availability of clinical end-point data. Even more

importantly, MRD might guide maintenance and consolidation strategies, thus making a step forward towards tailored treatment strategies in this disease.

Available data suggest that a maintenance approach using alemtuzumab may cause considerable myelotoxicity, lymphocytopenia, and sometimes life-threatening infections, in particular if conventional doses of alemtuzumab are administered within 3 to 6 months after the last chemotherapy in subjects with a low tumor load41,42.

The rationale to investigate lenalidomide maintenance treatment is described in section 2.1.

2. Objectives of the Clinical trial

2.1. Rationale for the clinical trial

Investigator-initiated studies have demonstrated that sequential use of CLL therapies (consolidation/maintenance) can improve the quality of response achieved with induction.[43] A limited number of maintenance regimens have been investigated with the best results obtained with the monoclonal antibodies alemtuzumab and rituximab, however the route of administration (IV) for both and the toxicity with alemtuzumab could hinder their acceptance and implementation as maintenance therapies[42,44-46].

Lenalidomide is an immunomodulatory drug that stimulates host-immunity by increasing the number of and stimulating the activity of T-cells and natural killer cells, which may be beneficial in the treatment of relapsed or refractory subjects with CLL - a disease typically characterized by profound immunosuppression[47-49 50]. Phase 1 studies[51] and two phase 2 studies of lenalidomide[50] monotherapy provided evidence of clinical activity in subjects with relapsed or refractory CLL with poor prognostic features, including high-risk cytogenetics and/or bulky disease[52,53]. A consolidation study of lenalidomide following pentostatin, cyclophosphamide and rituximab (PCR) as first line therapy demonstrated improvement in quality of response[54]. Treatment consisted of 6 cycles of PCR and all subjects completing 6 cycles underwent complete restaging and evaluation for MRD using flow cytometry. Following restaging and adequate recovery of blood counts, subjects received 6 months of lenalidomide consolidation by continuous daily administration. The starting lenalidomide dose was 5 mg/day with escalation to 10 mg/day after the first cycle as tolerated. Subjects again underwent complete restaging and MRD evaluation after 6 months of lenalidomide. At the time of this restaging, MRD negative subjects entered observation. Those with residual disease continued on lenalidomide and underwent repeat MRD assessment every 3 months with cessation of lenalidomide when an MRD negative state achieved. Forty-four (44) subjects were eligible for treatment: 71% male, median age 65 (range 44-78); intermediate Rai risk 61%; high Rai risk 39%. On prognostic testing 32% were CD38+, 52% Zap-70+, 52% IGHV unmutated, and 16% had high risk FISH (del 17p13; del 11q22). Thirty-eight (38) of 44 eligible subjects (86%) completed 6 cycles of PCR induction. The response rate to induction was 98% with 15 CR/CRi, 3 CCR, 9 nPR and 16 PR. Four subjects with CR became also MRD negative. Thirty-four (34) initiated lenalidomide consolidation. Among the 34 subjects who initiated consolidation, the median number of cycles of lenalidomide received was 5.5 (range 1-19). Adverse events deemed at least possibly related to lenalidomide consolidation included 22 (65%) subjects with Grade 3+ hematologic toxicity and 4 (12%) with grade 3+ non hematologic toxicity. Among the 34 subjects who received at least 1 cycle of lenalidomide, 4 subjects improved the quality of their response to date with 11 subjects still on lenalidomide. After median follow-up of 16 months, 42/44 subjects are alive and median duration of response has not been reached. To date 3/44 (7%) of subjects have progressed to require additional treatment.

CLLM1 is a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of lenalidomide administered as maintenance treatment to subjects with CLL who have responded to first-line therapy (induction) achieving a response of at least PR and are at high risk of early progression[27]. This study will compare the efficacy of lenalidomide maintenance treatment versus placebo

at prolonging PFS; and as secondary endpoints assess overall survival, the safety of lenalidomide treatment and evaluate MRD kinetics in peripheral blood whilst subjects are on maintenance.

Although maintenance therapy has been established in recent years for the treatment of a subset of subjects with Non-Hodgkin's Lymphoma (NHL), it is a novel concept in the management of CLL. It is not regularly used and only a limited number of small studies have been conducted evaluating consolidation/maintenance therapy for limited periods of time with alemtuzumab or rituximab. Based on the limited amount of available data, it appears that maintenance therapy may improve the quality of remission in CLL subjects and prolong progression-free survival (PFS)[42,43,55,56]. A large phase 3 trial investigating lenalidomide as maintenance following response to second line therapy is ongoing. However, a large well-controlled study has not been conducted to investigate the beneficial effect of maintenance therapy following front line therapy; specifically in subjects with aggressive disease. This phase 3 study will evaluate whether lenalidomide maintenance therapy will prolong PFS in CLL subjects with a high risk of early progression following first line treatment.

2.2. Primary objective

To compare the efficacy of lenalidomide versus placebo maintenance therapy.

The primary efficacy objective of this study is to investigate if lenalidomide maintenance therapy is supersior to placebo maintenance therapy in prolonging PFS, for subjects with a high risk of early progression following first-line treatment. All subjects, including both subjects who do and do not achieve MRD negativity will be treated up to disease progression with maintenance.

2.3. Secondary objective

- To evaluate the prolongation of overall survival (OS) of lenalidomide versus placebo maintenance therapy.
- To evaluate the safety of lenalidomide versus placebo maintenance therapy.

2.4. Study Endpoints

2.4.1. Primary

- Progression-Free Survival (PFS) based on assessment of an independent review committee

2.4.2. Secondary

- Progression-Free Survival (PFS) based on investigator's assessment
- Progression-free survival based on investigator's assessment censoring subjects who started new anti-leukemic therapy before disease progression
- Overall Survival (OS)

- Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide or placebo], premature withdrawals
- MRD levels (Evaluation of minimal residual disease (MRD) by flow cytometry and comparison between MRD levels immediately after the completion of first line therapy to levels 6 cycles, 12 cycles, 18 cycles, 24 cycles and subsequently annually during treatment with lenalidomide or placebo). It is anticipated that some subjects who are randomized to the lenalidomide arm, will further decrease MRD levels over the duration of treatment in contrast to the subjects randomized into the placebo arm
- Health-Related Quality of Life by EORTC QLQ C30 and EQ-5D
- Time to next treatment
- Event-free survival
- Treatment free survival after 2nd line treatment

2.4.3. Exploratory

- Only for patients who underwent pre-screening procedures before activation of amendment 3: Cytogenetic fluorescence in situ hybridization (FISH), Biomarker analyses (Zeta-chain-associated protein kinase 70 [ZAP 70], CD38 and IGHV mutational status and immune cell analyses (NK and T cells)
- Thymidine kinase, Beta-2 Microglobulin (β2M)
- Genetic or biological markers of predictive value with regard to study endpoints

3. Organizational and administrative aspects of the trial

3.1. Sponsor and Sponsor's representative

Sponsor: University of Cologne
Albertus-Magnus-Platz
50923 Cologne
Germany

Responsible Coordinating Physician and Sponsor's representative: Dr. Anna Fink, Department I of Internal Medicine of the University Hospital Cologne and Central Study Office of the German CLL Study Group, Kerpener Str. 62, 50924 Cologne, Germany.

Global Principal Investigator: PD Dr. Barbara Eichhorst, Department I of Internal Medicine of the University Hospital Cologne, Kerpener Str. 62, 50924 Cologne, Germany.

3.2. Chairman of the German CLL Study Group

Director of the Deapartment I of Internal Medicine and Chairman of the GCLLSG: Prof. Dr. Michael Hallek, Department I of Internal Medicine of the University Hospital Cologne, Kerpener Str. 62, 50924 Cologne, Germany.

3.3. Statistics

Statistician: Dr. Dipl.-Math. Jasmin Bahlo
Department I of Internal Medicine of the University Hospital Cologne, Kerpener Str. 62, 50924 Cologne, Germany

3.4. Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board made up of independent experts will be set up. It will consist of experts who are not involved in the conduct of the trial according to the DSMB charter. The primary and overriding concern of the DSMB is to ensure that subjects are not put at undue risk, while participating in study CLLM1. Specifically this includes:

(i) Monitoring the safety data of the subjects at least twice a year until 28 days after the last dose of trial treatment has been received by the last randomized subject or until the study is concluded; whichever is shorter.

(ii) Advising the sponsor/GCLLSG should such data suggest to the DSMB that the trial be modified or prematurely terminated.

Throughout this process of surveillance, the DSMB provides the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected. The data necessary for the DSMB to fulfill this function are provided by the sponsor as determined by the DSMB charter. Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the

DSMB considers necessary at least every 6 months. A list of the members of the DSMB is given in Appendix 11.4.

3.5. PFS Independent Review Committee

An independent PFS Review Committee will perform a blinded, independent assessment of the documented progressive disease prior to database lock. The members of the PFS Independent Review Committee will be determinded and contact details given in Appendix 11.2.

3.6. Central laboratory assessments

All tests performed in the context of the central laboratory assessments will be performed free of charge for the participating sites and investigators and the results will be sent to them. Shipping costs will be reimbursed with the documentation fee. Names of responsible persons and shipping address are included in the appendices section 11.5.

3.6.1. Molecular cytogenetics

If required, the central molecular genetics reference testing at the GCLLSG molecular cytogenetics reference laboratory in Ulm (fluorescence in situ hybridization (FISH), mutation status of TP53, and IGHV, may be performed at Screening:In the event of relapse/progression a further sample should also be submitted from each subject for follow-up examination.For subjects with MRD levels of ≥10^{-4} but <10^{-2} but with missing cytogenetic results for IGHV status, FISH and TP53, a blood sample consisting of 20-40 ml peripheral heparinized blood should be obtained.

Material required

20-40 ml peripheral heparinized blood (40 ml for subjects with slightly increased lymphocyte counts) (Blood/BM: heparin = 10:1) are to be sent (for contact details see appendix 11.5) with the appropriate form.

Please note that the full amount of 40 ml is needed for all subjects with slightly increased lymphocyte counts (<$10x10^9$/l) to ensure that screening analyses can be performed successfully.

3.6.2. MRD testing and T-/NK-cell analyses

Subjects are examined by quantitative highly sensitive flow cytometry (MRD flow) for the presence of minimal residual disease (MRD) at the GCLLSG MRD reference laboratory in Kiel. Based on MRD flow, the exact number of remaining CLL-cells after therapy can be determined.

MRD assessments of peripheral blood are to be performed at screening (to assess the eligibility for CLLM1) in all registered subjects who achieved a response after the first line treatment (at least PR) and after 6 cycles, 12 cycles, 18 cycles, 24 cycles of treatment and then annually to guide dose escalations of lenalidomide for subjects who still present with MRD levels ≥ 10^{-4} in peripheral blood.

In subjects who are eligible for CLLM1 (high risk subjects at screening defined by either peripheral blood MRD ≥ 10^{-2} or MRD < 10^{-2} to ≥ 10^{-4} plus at least one of the following parameters: deletion 17p,TP53 mutation or unmutated IGHV) the efficacy of lenalidomide maintenance will be evaluated with MRD. In those randomized subjects additional MRD assessments have to be performed in peripheral blood after 6 cycles, 12 cycles, 18 cycles, 24 cycles and then annually (after 36, 48 and 60 months) in peripheral blood until progression or up to the end of the study.

If clinically indicated, MRD assessments in bone marrow are scheduled between screening randomization (i.e. prior to initiation of maintenance or placebo in order to assess primary tumor load). After 12 cycles and 18 cycles on maintenance, a repeated bone marrow assessment is advised. The decision for the repeat bone marrow assessment is at the discretion of the investigator.

T- and NK-cell analyses will be done in order to investigate the composition of T- and NK cell subpopulations after induction therapy, the changes induced into T- and NK cell subpopulations induced by lenalidomide maintenance vs. in the placebo arm. T- and NK cell subpopulation composition and changes will be related to PFS, response, MRD kinetics and toxicity of the drug.

Material required:

2 x 10 ml heparinized peripheral blood and 1 x 10 ml EDTA blood at screening, plus after 6 cycles, 12 cycles, 18 cycles, 24 cycles of treatment and then annually whilst on maintenance or placebo plus 5 ml BM aspirate in heparine (at screening and after 12 cycles and 18 cycles (at the discretion of the investigator) on maintenance therapy only) are to be sent within 48 hours (for contact details see appendix 11.5) with the appropriate form.

3.6.3. Immunophenotyping, CD38/ZAP-70 Expression and karyotyping

Only for patients who underwent pre-screening procedures before activation of amendment 3: The central reference testing of immunophenotyping for confirmation of diagnosis, of CD38 and Zap-70 expression as well as karyotyping will be performed at the hematological laboratory of Cologne University Hospital at pre-screening. Peripheral blood samples are to be sent to the shipping address together with the appropriate form. The immunophenotyping will be performed within the pre-screening procedure before start of the first line treatment.

Material required:

1 x 9 ml EDTA anticoagulated blood and 1 x 9 ml of Heparin anticoagulated blood are to be sent within 48 hours to the shipping address together with the appropriate form.

3.6.4. Bone marrow biopsy

Bone marrow biopsy including aspirate may be analyzed at the time point before the start of the maintenance therapy to confirm the response to first line treatment. The bone marrow biopsy will be analyzed centrally at the Institute for Pathology University Hospital Kiel. The bone marrow punch of at least 1 cm length is immediately transferred to 4% formalin solution (pH 7.5) has to be sent with the appropriate form and a referral (if possible) to the shipping address.

Material required:

Bone marrow punch of at least 1 cm length in 4% formalin solution (pH 7.5).

(To save shipment costs the material will be sent together with the material for MRD Analysis to the MRD reference laboratory in Kiel. The trephine biopsy will be forwarded free of charge to the Institute for Pathology at the University Hospital Kiel)

3.6.5. Serum parameters (thymidine kinase, β2 microglobulin)

Only for patients who underwent pre-screening procedures before activation of amendment 3: The testing of the serum parameters (thymidine kinase, ß2-microglobulin) as supporting scientific research will be performed at the Institute of Clinical Chemistry of the University Hospital of Cologne. 10 ml whole blood (for extraction of 5ml serum) is to be sent to the shipping address together with the appropriate form.

Material required:

5 ml serum (10 ml whole blood for extraction of serum)

3.7. Central organization units

Project management:	Central Study Office of the German CLL Study Group, Gleueler Str. 176, 50931 Cologne, Germany, cllstudie@uk-koeln.de
Monitoring:	Kompetenznetz Maligne Lymphome, Kerpener Str. 62, 50924 Cologne, Germany
Data management:	Central Study Office of the German CLL Study Group, Gleueler Str. 176, 50931 Cologne, Germany, cllstudie@uk-koeln.de
SAE management:	Central Study Office of the German CLL Study Group, Gleueler Str. 176, 50931 Cologne, Germany, cllstudie@uk-koeln.de
Medical management:	Central Study Office of the German CLL Study Group, Gleueler Str. 176, 50931 Cologne, Germany, cllstudie@uk-koeln.de

Investigators and trial sites

This clinical trial will be carried out as a randomized, multicentre, double-blind trial at about 200 trial sites. If necessary, further qualified trial sites may be recruited to the trial.

A list of trial sites involved, including information on the principal investigators, further investigators, and trial staff, will be kept and continuously updated. A list of the trial sites with names of the principal investigators is given in Appendix 11.1.

Requirements for investigators and trial sites

In this trial, sites will be selected with experience in the treatment of chronic lymphocytic leukemia and the conduct of hemato-oncological trials, preferably with the experience of a registration trial. GCLLSG sites will be contacted and the feasibility for this trial will be evaluated with a questionnaire. Only physicians are allowed to be investigators in this trial.

The clinical trial will be financed by a grant from Celgene International Sarl, Boudry, Switzerland.

4. Trial conduct

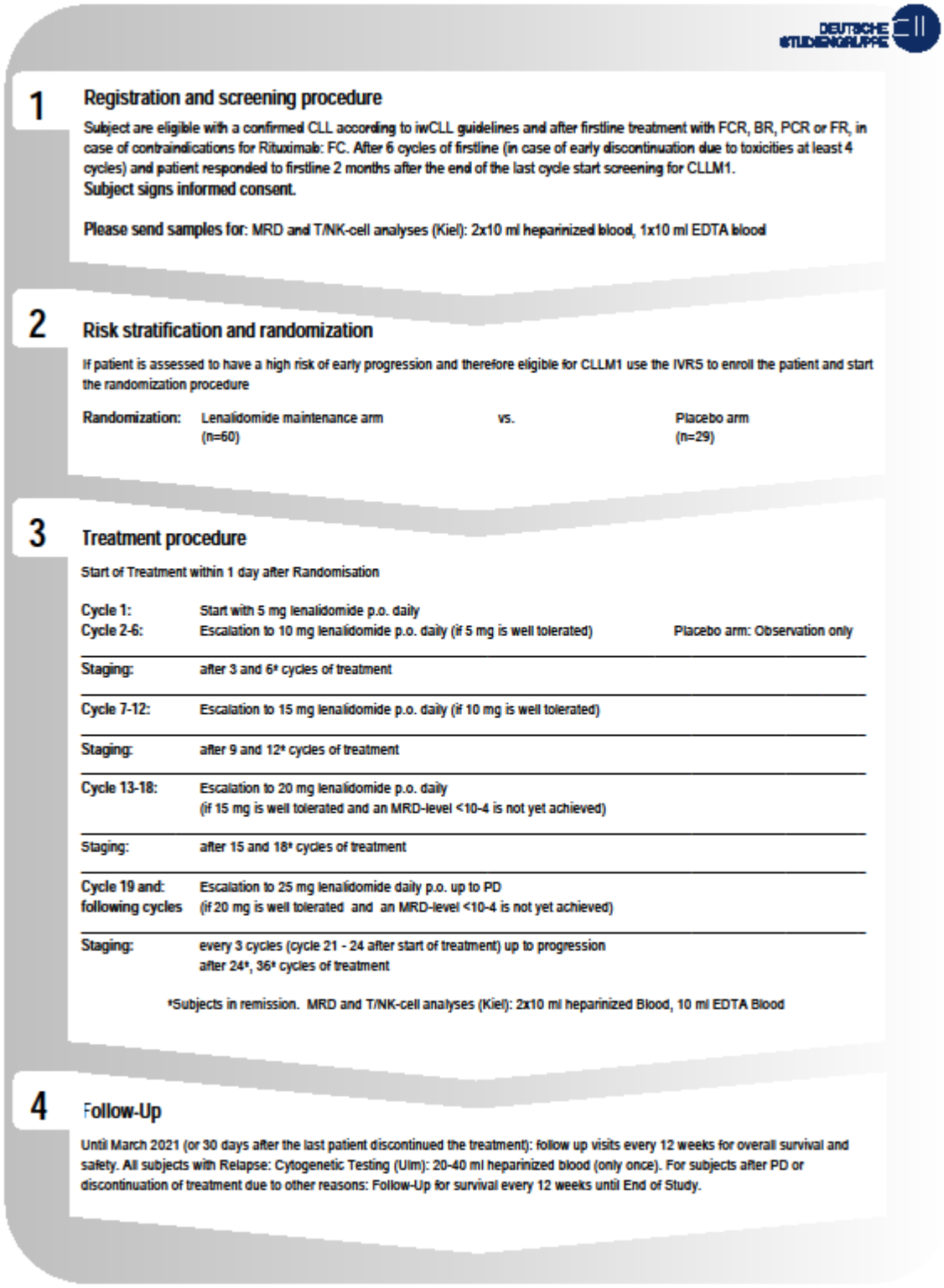

Figure 1: Trial conduct

4.1. General aspects of trial design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that compares the efficacy and safety of oral lenalidomide (Revlimid®) maintenance therapy to that of placebo maintenance therapy in high-risk subjects with CLL who have achieved a response of at least PR and either:

a.) have MRD levels in the peripheral blood at final restaging of $\geq 10^{-2}$

b.) or have MRD levels in the peripheral blood at final restaging of $\geq 10^{-4}$ - $< 10^{-2}$ combined with at least one of the three following parameters:

- an unmutated IGHV-status
- or 17p-deletion
- or TP53 mutation

after first line therapy with FCR, FR, BR, Pentostatin-CR or FC (in case of hypersensitivity reactions to Rituximab).

4.1.1. Time plan

Table 1: Time plan of the trial

First subject first visit (FPFV):	2Q 2012
Last subject first visit (LPFV):	1Q 2016
Last subject last visit (LPLV):	Expected 1Q 2021
Final study report:	Expected 1Q 2022

Table 2: Study Assessment Plan

Procedure: All study procedures should be performed within ± 7 days of the scheduled visit unless otherwise stated.	ICF/ Inclusion/ Exclusion and Spitzer-Index	Medical History includes regimen, no. of cycles, reason for early discount. of firstline, if applicable, and ongoing AEs	Pregnancy test and pregnancy and risk counselling (mandatory within the maintenance treatment period)	CIRS, calculated creatinine clearance (Cockcroft-Gault)	ECOG/ WHO Performance-Status/ Evaluation of ß-symptoms	Physical examination: lymphadenopathies, spleen and liver	Vital signs including weight	Hematology	Immunoglobulines (IgA, IgM, IgG, IgE)	Chemistry basic: alkalinephosphatase, (AP), total bilirubin, AST/ SGOT, ALT/ SGPT, LDH, and uric acid	Chemistry extended : basic chemistry plus sodium, potassium, chloride, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein	Assessment of AIHA (direct antiglobulin Test)	HIV ,HBV and HCV tests	Thyroid function test (TSH, T3 and T4 levels)	ECG (12 lead)	Central Lab (MRD:sixmonthly up to month 24, then annually - T/ NK-cell analyses: during follow up month 6 and month 12	Optional: Central Lab: Bone Marrow Aspirate and Biopsy	Optional: Central Lab (mol. Cytogenetics)	CT scans (chest, abdomen and pelvis, if clinically indicated)	Tumor lysis monitoring	Study drug administration: Study drug to be dispensed in 28-day cycles. Unused studydrug to be returned every 28 days	AEs, SAEs (after discontinuation of treatment only SAE)	Assessment of response	Concomitant medication	Survival	Secondary malignancies	Quality of life (sixmonthly during treatment, after discontinuation of treatment annually)
Screening (2-5 months after firstline treatment)	X	X	X[a,b]	X	X	X[c]	X[d]	X[e]	X		X	X[f]	X	X	X[g]	X[i]	X[j]	Xt	X	X[l]			X[n]	X			X[r]
Day 1 cycle 1 and day 1 of each first cycle with escalated dose			X[a,b]		X		X[d]	X[e]		X										X[l]	X	X[m]		X		X[q]	
Day 8 and 15 for cycle 1 and each first cycle with escalated dose							X[d]	X[e]		X										X[l]		X[m]				X[q]	
Every 28 days (4 weeks): day 1 of each cycle			X[a,b]		X		X[d]	X[e]		X											X	X[m]				X[q]	
Every 3 cycles during treatment			X[a,b]		X	X[c]	X[d]	X[e]		X					X[g]				X		X	X[m]	X[n]	X		X[q]	X[r]
Every 6 cycles during treatment			X[a,b]		X	X[c]	X[d]	X[e]			X			X	X[g]	X[i]	X[j]		X		X	X[m]	X[n]	X		X[q]	X[r]
Progression of disease or treatment discontinuation			X[a,b]		X	X[c]	X[d]	X[e]	X	X				X				X[k]	X			X[m]	X[n]	X[p]		X[q]	X[r]
Every 3 months after Tx discontinuation					X[s,o]	X[c,o]		X[s,o]		X[s,o]												X[m,o]	X[n,o]		X[p,o]	X[q,o]	X[r,o]

a. Females of childbearing potential (FCBP) (this protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months i.e. has had menses at any time in the preceding 24 consecutive months). must have a medically supervised pregnancy test (serum or urine with sensitivity of at least 25 mIU/mL). FCBP must have 2 negative pregnancy tests prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the investigator has verified that the results of these pregnancy tests are negative (see Appendix 11.17. For additional information about the frequency and schedule of pregnancy testing, see the document “Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods” in Appendix 11.18. For requirements regarding: 1) counseling and education of subjects, including the reading of the “Lenalidomide Information Sheet” by the subject; 2) reliable contraception methods; and 3) retention of Risk Management Plan documents concerning the pregnancy prevention program, see Appendix 11.19 and Appendix 11.20.

b. All male and FCBP subjects must be counselled about pregnancy precautions and risks of fetal exposure. All subjects must also be counselled against sharing study drug and donating blood (or semen for males) during and within 28 days of discontinuing study drug (see Table 2 Study Assessment Plan: Visit schedule. for frequency).

c. The physical examination of lymphadenopathy will be recorded with the diameter, in two dimensions, of the largest palpable nodes in each of the following sites: cervical, axillary, inguinal. Physical examination of the spleen and liver will be recorded in cm below costal margin (for liver in the medioclavicular line)

d. Vital signs include: temperature, pulse, blood pressure, weight and height (height to be measured at screening only)

e. Hematology includes WBC, Hb, HCT, MCV differential, platelet count, ANC, ALC, and reticulocyte count. Prolymphocytes should be done at screening and in case of progressive disease at the discretion of the investigator.

f. DAT (direct antiglobulin test) will be performed and analyzed in the local laboratory at time of screening. The DAT test must be repeated if the investigator suspects hemolytic anemia during the course of the study.

g. ECG will be performed and interpreted locally at time of at screening, after every 6 cycles and at treatment discontinuation. Pretherapeutically the evaluation will be done according to the Cumulative Illness Rating Scale. Reevaluation every six months and at treatment discontinuation; Changes will be captured as new concomitant disease or AE.

h. Only for patients who underwent pre-screening procedures before activation of amendment 3: Serum thymidine kinase and β2M will be analyzed during Pre-Screening at a central laboratory.

i. Flow cytometry for MRD status will be performed at a central laboratory. Peripheral blood will be drawn at screening (after first line treatment) and for all subjects still in remission after 6 cycles, 12 cycles, 18 cycles, 24 cycles and then annually. For all subjects results of MRD after 12 and 18 cycles should be used to define if dose of lenalidomide can be escalated after 12 and 18 cycles of treatment. T- and NK-cell analyses will be performed centrally (Lab Kiel) at Pre-Screening (peripheral blood), Screening (peripheral blood and bone marrow), after 6 cycles and after 12 cycles (peripheral blood and bone marrow, if available) of treatment.

j. Bone marrow aspirate and biopsy will be optionally performed before randomization (after firstline treatment) and might be repeated after 12 and 18 months of treatment. Bone marrow aspirate and biopsy review as well as flow cytometry for MRD status will be performed at a central laboratory.

k. In the event of relapse/progression a sample for central molecular genetics reference testing at the GCLLSG molecular cytogenetics reference laboratory in Ulm should be submitted from each subject for follow-up examination.

l. In subjects with remaining bulky disease (at least one lymph node of more than 5 cm in the largest diameter) at the time of screening tumor lysis prophylaxis, consisting of 300 mg allopurinol/day and oral hydration will be administered for **3 days prior to starting treatment** and for at least the first

cycle of each dose level. If response assessments confirm the absence of bulky disease, it is allowed to stop tumor lysis prophylaxis.

m. Adverse events that lead to study discontinuation should be followed until resolution or stabilization. Serious adverse events should be monitored for 30 days after the last study specific procedure. All SAEs should be followed until resolution or stabilization. Any SAE deemed by the investigator to be related to study drug should be reported and followed until resolution. Infections during treatment should be reported on the AE pages, infections during the follow up should be reported on the SED pages of the CRF. AEs that should not be reported are described in section 4.13

n. Investigators have to provide assessment of CR, CRi, nPR, PR and PD based on laboratory, physical exam, and if available appropriate bone marrow aspirate/biopsy and CT scan findings.

o. Those subjects who discontinue maintenance therapy for reasons other than disease progression (i.e. unacceptable toxicity) should be followed every 3 months until PD; for those subjects, study visits and serial measurements of efficacy will continue to be performed, however some safety evaluations are no longer required to be performed (including thyroid function tests, pregnancy status, adverse event collection, concomitant medication collection); however SAEs related to study drug or procedures will continue to be recorded up to end of study. All AEs (all CTC grades) will be reported up to 28 days after the last dose of IMP.

p. Subjects who develop PD or disease transformation (Richter's syndrome or prolymphocytic leukemia), at any time, will be followed up every 3 months for survival, subsequent CLL therapies, second primary malignancies, hospitalizations and will complete QoL-questionnaires at defined time points. Subjects who discontinue from progression follow up for reasons other than progression/disease transformation should still be followed for survival. If possible, date of progression and documentation of progression should be collected for these subjects. Subjects will be followed until end of the study (or died/ become lost to follow up before end of study or until at least 118 events (progression or death) have occurred).

q. Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of the start of the study treatment and including the survival follow up period. Subjects will be followed until end of study from randomization of the first patient (or subject died/ become lost to follow up before 5 years) or until at least 118 events have occurred, whichever comes later. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria applies; these events must also be documented in the appropriate page(s) of the CRF (AE pages and SED page) and subject's source documents. Documentation of the second primary malignancy must be provided with the reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.) Secondary malignancies occurring between signing the ICF and before the start of the study treatment will be considered as exclusion criteria and will be recorded on the CIRS page and should be ticked as exclusion criterion on the prescreening/screening pages.

r. EORTC QoL Questionnaires and the Euro Qol EQ 5D will be completed by the subject at time point of randomization (after firstline therapy but before the start of maintenance treatment), after 6 and 12 months of treatment, and then on an annual basis until March 2021, at the time point of discontinuation of treatment and after discontinuation on an annual basis until March 2021.

s. These test within the follow-up should only be performed for subjects without progressive disease and should not be done for subjects in the follow up with documented progressive disease.

t. For subjects with MRD levels of$\geq 10^{-4}$ but $<10^{-2}$ but with missing results for the IGHV status, a blood sample consisting of 20-40 ml peripheral heparinized blood should be obtained and send for analysis to the central lab in Ulm/Germany.

4.2. Discussion of trial design

CLLM1 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that will compare the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo maintenance therapy in high-risk subjects with CLL who have achieved a response of at least PR and either have MRD levels in the peripheral blood at final restaging of $\geq 10^{-2}$ or MRD levels in the peripheral blood at final restaging of $\geq 10^{-4}$ - $<10^{-2}$ combined with an unmutated IGHV-status or 17p-deletion or TP53 mutation after first line therapy. The randomization and double-blind design eliminates potential bias in subject selection and data interpretation. In CLL, prolongation of PFS due to maintenance therapy and improvement of the quality of response achieved at the end of first-line treatment is a recent concept. Only a few small studies evaluating consolidation and / or maintenance therapy for limited periods of time with alemtuzumab or rituximab have shown improvement in the quality of response and prolongation of progression free survival. A large phase 3 trial investigating lenalidomide as maintenance following response to second line therapy is ongoing. This phase 3 study will evaluate whether lenalidomide maintenance therapy will prolong PFS in CLL subjects with a high risk of early progression following first line treatment. The study will also compare the effect of lenalidomide versus placebo on improvement of OS as a secondary endpoint. Additional exploratory endpoints will be analyzed to detect potential predictive factors for the response to lenalidomide maintenance treatment.

4.3. CIRS Score

Various scores for systematic evaluation of the comorbidity of geriatric oncological subjects have been developed and evaluated over the last decades[57,58]. In the CIRS (Cumulative Illness Rating Scale) score the number and severity of the existing comorbidities are qualitatively documented and quantified[59]. Several studies have documented a high reliability and validity of the CIRS score[60]. For a geriatric non-oncological subject population CIRS threshold scores have been defined which permit differentiation of different subject groups with different risks of hospitalization and mortality[61]. In some more recent studies the extent of comorbidity as determined by the CIRS score has proved to be prognostically relevant for the overall survival of tumor subjects[62]. Two further studies also describe the distribution of CIRS scores in a sample of older cancer subjects with different cancers[63,64]. In about half the subjects studied a total CIRS score of 0-6 (= no to mild comorbidity) was determined, while in the other half the total CIRS score was 7-18 (= moderate to high comorbidity)[63]. A CIRS threshold of 6 thus may be a suitable risk discriminator in CLL subjects. With the help of the CIRS score the extent of comorbidity of a potential study subject can be assessed qualitatively and quantitatively with relatively little effort before the subject is admitted to the study.

The form with precise instructions on calculation of the CIRS score is attached at the end of the protocol (Appendix 11.11) and must be submitted on registration of the subjects.

4.4. Selection of trial population

For this study physically fit subjects (as defined by CIRS score) are eligible with a confirmed diagnosis of a chronic lymphocytic leukemia according to the IWCLL guidelines, and treated with a first line treatment of FR, FCR, BR, Pentostatin-CR or FC (in case of contraindications for rituximab). Subjects must have achieved a response of at least PR subsequent to first line therapy and fulfill the criteria of high risk of early progression. These criteria are defined as:

- MRD levels in the peripheral blood at final restaging of either ≥10^{-2} after first line therapy or
- MRD levels in the peripheral blood at final restaging ≥10-4 - <10^{-2} after first line therapy combined with at least one of the following three parameters:
    - an unmutated IGHV-status
    - or 17p-deletion
    - or TP53 mutation.

Reasons for gender distribution

It is expected, that both study arms will have the same percentage of male and female subjects. Subjects will therefore not be stratified by gender, the distribution will allow to detect gender-specific differences in efficacy or safety.

4.4.1. Inclusion criteria

1. Must understand and voluntarily sign an informed consent form.
2. Age ≥ 18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia[1].
5. Must have been treated with one of the first line induction therapies: fludarabine/cyclophosphamide, fludarabine/rituximab, fludarabine/cyclophosphamide/rituximab, pentostatin/cyclophosphamide/rituximab or bendamustine/rituximab.
6. Must have achieved a response of at least PR ((IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia)following completion (minimum 4 cycles) of first line induction therapy prior to randomization, and have either:
    - MRD levels in the peripheral blood at final restaging of ≥10^{-2} or
    - MRD levels in the peripheral blood at final restaging of ≥10^{-4} - <10^{-2} combined with an unmutated IGHV-status or 17p-deletion or TP53 mutation.
7. Must have completed last cycle of at least 4 cycles of first-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization.
8. Subjects who completed first-line induction treatment with less than 6 cycles but at least 4 cycles should document reason for early discontinuation.
9. Must have an Eastern Cooperative Oncology Group (ECOG see appendix 11.13) performance status score of ≤2.

10. Negative serological Hepatitis B test or negative PCR in case of positive serological test without evidence of an active infection, negative testing of Hepatitis C RNA, negative HIV test within 6 weeks prior to randomization.
11. Females of childbearing potential (FCBP)† must:
    - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices complete and continued sexual abstinence.
    - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, two reliable forms of effective contraception simultaneously to achieve a PEARL-Index <1 without without interruption (Highly effective methods: Intrauterine device (IUD), Hormonal (birth control pills, injections, implants), Tubal ligation, Partner's vasectomy, Additional effective methods: Male condom, Diaphragm, Cervical Cap). 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
12. Male subjects must:
    - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy.
    - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy.
13. All subjects must:
    - Have an understanding that the study drug could have a potential teratogenic risk.
    - Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy.
    - Agree not to share study medication with another person.
    - Be counseled about pregnancy precautions and risks of fetal exposure.
14. Willingness to inform the general practicioner

4.4.2. Exclusion criteria

1. A CIRS Score of more than 6 or a single score of 4 for an organ system limiting the ability to receive an intensive treatment
2. Active infections requiring systemic antibiotics.
3. Systemic infection CTC grade 3 or 4 that has not resolved > 2 months prior to randomization in spite of adequate anti-infective therapy.
4. Autologous or allogeneic bone marrow transplant as first line therapy.
5. Pregnant or lactating females.

† Definition: This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

6. Systemic treatment for CLL in the interval between completing the last cycle of first-line induction therapy and randomization.
7. Participation in any clinical study or having taken any investigational therapy which would interfere with the study drug for a disease other than CLL within 28 days prior to initiating maintenance therapy.
8. Known presence of alcohol and/or drug abuse.
9. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization.
10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
11. History of renal failure requiring dialysis.
12. Prior therapy with lenalidomide.
13. Any of the following laboratory abnormalities:
    - Calculated (method of Cockroft-Gault) creatinine clearance of <60 mL/min
    - Absolute neutrophil count (ANC) < 1,000/µL (1.0 X 109/L)
    - Platelet count < 50,000/µL (50 X 109/L)
    - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN)
    - Serum total bilirubin > 2.0 mg/dL (with the exception of Gilbert's Syndrome)
14. Uncontrolled hyperthyroidism or hypothyroidism.
15. Venous thromboembolism within one year.
16. ≥ Grade-2 neuropathy.
17. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.
18. Disease transformation (active) (i.e. Richter's Syndrome, prolymphocytic leukemia).
19. Known allergy to allopurinol if the subject has bulky disease.
20. Prisoners, or subjects who are institutionalized by regulatory or court order or persons who are who are in dependence to the sponsor or an investigator.

4.5. Withdrawal of trial subjects after trial start

Investigators will make every reasonable effort to keep each subject on the study until all planned treatments and assessments have been performed. Study drug treatment may be discontinued for the reasons listed below. When a subject ends the treatment phase of the study, the date and reason for early treatment discontinuation will be noted in the source document and the appropriate pages of the CRF. The investigator will inform the study office of the German CLL Study Group about the early withdrawal within seven days. Investigators will make any reasonable effort to collect and report end-of-treatment evaluations and follow-up evaluations.

The end-of-treatment evaluation should be performed before any other therapeutic intervention. Regardless of the reason for termination, all data available for the subject at the time of discontinuation from the study should be recorded in the CRF, and all reasons for discontinuation of treatment must be documented in subject records. Subjects who discontinue study treatment prematurely for reasons other than PD, in particular female subjects who discontuinue study treatment due to pregnancy, will continue to be followed for response assessment until PD occurs. Subjects who develop PD (including disease transformation) and subjects who discontinue the progression free follow up phase prior to progression/disease transformation will enter the survival follow up period. Subjects will be followed for the total duration of the study: 72 months or died/become lost to follow up before the 72 months and until at least 118 events have occurred.

4.6. Withdrawal from treatment

The following events are considered sufficient reasons for discontinuing a subject from study drug:

- Pregnancy in a female subject
- AEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Disease progression with or without histological transformation
- Subject withdraws consent
- Subject lost to follow-up
- Death
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the subject's medical records. The sponsor has to be notified of all discontinuations from study drug.

4.7. Withdrawal from documentation

- Subject withdraws consent

4.8. Closure of trial sites/premature termination of the clinical trial

4.8.1. Closure of trial sites

The sponsor and the sponsor's representative have the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Non-compliance with GCP

- Failure to adhere to the study protocol

4.8.2. Premature termination of trial

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or for reasonable administrative reasons. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which must be documented. The Global Principal Investigator must be informed without delay if any investigator has ethical concerns about continuation of the trial.

4.9. Long term follow up for survival and late toxicities following the end of the study

Each subject will additionally be informed about the importance of long term follow up data and asked for his consent to the long term follow up within the GCLLSG registry trial. Within the non-interventive GCLLSG registry trial the observation will be continued after end of the CLLM1 study in 2021 since the primary end-point in the CLLM1 study is progression-free survival (PFS). However, the overall survival is a clinically important secondary endpoint in CLLM1. Therefore it is essential to report both overall survival and PFS. In addition, late toxicities, such as MDS or AML, EBV-associated lymphoproliferative disease or Hodgkin`s disease, late opportunistic infections and second primary malignancies, are increasingly seen and are likely to differ depending on the intensity of therapy. Moreover, meta-analysis of several phase 3 trials with long follow-periods are desirable. The sponsor has ongoing responsibility for safety reporting for their trials and for any late safety aspects. In addition unless the trials have long-term follow-up any late beneficial effects of the therapies will be lost.

If a subject agrees to participate in the GCLLSG registry trial he will be annually followed up for disease progression, subsequent CLL therapies, secondary malignancies, late toxicities and overall survival.

4.10. Treatment

4.10.1. Maintenance Therapy

Table 3: Escalation schedule

dose	Cycle 1	Cycle 2-6	Cycle 7-12	Cycle 13-18	Cycle 19-progression
L- Dose	5 mg daily of a 28-day cycle	10 mg daily of a 28-day cycle	15 mg daily of a 28-day cycle	For patients who achieve MRD negativity after the 12th cycle: 15 mg daily of a 28-day cycle For all MRD positive patients: 20 mg daily of a 28-day cycle	For patients who achieve MRD negativity after the 12th cycle: 15 mg daily of a 28-day cycle For patients who achieve MRD negativity after the 18th cycle: 20 mg daily of a 28-day cycle For all MRD positive patients: 25 mg daily of a 28-day cycle

Study treatment for each subject begins the same day after the subject undergoes randomization. Lenalidomide is administered orally (identically-matched capsules). Subjects will receive lenalidomide 5 mg once daily on Days 1 through 28 of the first 28-day cycle. If the 5 mg dose is well tolerated (subject does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity [Grade 1 or 2] found to be unacceptable by the investigator or the subject), subjects should be escalated starting at the second cycle to 10 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression. If a subject develops a Grade 1 or 2 adverse event deemed unacceptable by the subject or investigator, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 5 mg dose level prior to escalation to the 10 mg dose level.

Subjects, who complete 5 continuous cycles at the 10 mg, may escalate the dose to 15 mg daily (cycle 7-12). If after 12 cycles of treatment a subject does not achieve a MRD level below 10-4 in peripheral blood and does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator or subject, the subject may be escalated to 20 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression. (starting with cycle 13 up to cycle 18).

If after 18 cycles of treatment a subject does not achieve a MRD level below 10-4 in peripheral blood and does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator or subject, the subject may be escalated to 25 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression (starting with cycle 19 up to disease progression).

Escalation to 20 mg and 25 mg respectively, are only allowed in subjects without any treatment interruption or any dose reductions in the previous cycles.

Dose interruptions/reductions are permitted for Grade 1 or 2 adverse events at the investigator's discretion. A guideline for the reduction of the dose of lenalidomide/placebo is provided. Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a toxicity deemed to be unacceptable by the investigator or subject.

Table 4: Dose De-escalation

L- Dose	5 mg daily of a 28-day cycle	10 mg daily of a 28-day cycle	15 mg daily of a 28-day cycle	20 mg daily of a 28-day cycle	25 mg daily of a 28-day cycle
Dose red. -1	2.5 mg daily of a 28-day cycle	5 mg daily of a 28-day cycle	10 mg daily of a 28-day cycle	15 mg daily of a 28-day cycle	20 mg daily of a 28-day cycle
Dose red. -2	2.5 mg eod of a 28-day cycle	2.5 mg daily of a 28-day cycle	5 mg daily of a 28-day cycle	10 mg daily of a 28-day cycle	15 mg daily of a 28-day cycle
Dose red. -3	n/a	2.5 mg eod of a 28-day cycle	2.5 mg daily of a 28-day cycle	5 mg daily of a 28-day cycle	10 mg daily of a 28-day cycle
Dose red. -4	n/a	n/a	2.5 mg eod of a 28-day cycle	2.5 mg daily of a 28-day cycle	5 mg daily of a 28-day cycle
Dose red. -5	n/a	n/a	n/a	2.5 mg eod of a 28-day cycle	2.5 mg daily of a 28-day cycle
Dose red. -6	n/a	n/a	n/a	n/a	2.5 mg eod of a 28-day cycle

Subjects experiencing a ≥ Grade 3 non-hematologic AE will have their study drug held until resolution of the AE as described in Table 5 Dose Reduction and Modification Guidelines. Subjects with a hematologic AE will modify study drug dosing as outlined in Table 5 Dose Reduction and Modification Guidelines. Subjects who have to discontinue treatment at any dose level for more than 35 days, have to discontinue the maintenance treatment and will be followed up for progressive disease. Subjects who cannot tolerate 2.5 mg eod x 28 days of a 28-day cycle are to be discontinued from study drug and followed for PD and survival as outlined in Figure 1.

Table 5: Dose Reduction and Modification Guidelines

NCI CTCAE Toxicity Grade	**Action**
Neutropenia ANC < 400/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when ANC recovers to ≥ 500/uL
Thrombocytopenia < 20,000/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when platelet count recovers to ≥ 25,000/uL

NCI CTCAE Toxicity Grade	Action
Syndromes	
Tumor Flare Grade 3 or 4	• Interrupt study drug therapy and initiate therapy with NSAIDs, narcotic analgesics or prednisone • Resume study drug (decrease one dose level) when symptoms resolve to ≤ Grade 2
Desquamating (blistering) rash	• Discontinue study drug
Non- desquamating rash Grade 3 Grade 4	 • Interrupt study drug therapy. • Resume study drug when the rash resolves to ≤ Grade 1 (decrease one dose level) • Discontinue study drug
Neuropathy Grade 3 Grade 4	 • If Grade 3, interrupt study drug therapy. • Resume study drug when the neuropathy resolves to ≤ Grade 1 (decrease one dose level) • If Grade 4, discontinue study drug
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; • Resume study drug when adequately anticoagulated (maintain dose level).
Hyperthyroidism or hypothyroidism	• Interrupt study drug and initiate appropriate medical therapy. • Resume study drug when appropriately controlled (maintain dose level).
Serum Creatinine Grade 1 **It is possible for subjects entering the study with a creatinine clearance ≥ 60 ml/min and a serum creatinine at the upper limit of normal to show slight fluctuations of the serum creatinine above the upper limit of normal. It is left at the investigator's discretion to measure the creatinine clearance for those subjects to evaluate whether a dose adjustment is needed.	 • Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 1, permanently discontinue and follow for PD • If at the end of the third week the creatinine level has improved to < Grade 1, resume study drug (maintain dose level) • If at the end of the third week the creatinine level has stabilized at Grade 1, resume study drug (decrease one dose level) • Following resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 2	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 2, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has improved to < Grade 1 resume study drug (maintain

NCI CTCAE Toxicity Grade	Action
	dose level) • If at the end of the third week, the creatinine level has improved to a Grade 1 or has stabilized at Grade 2, resume study drug (decrease one dose level)
	• Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 3	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 3, or if dialysis is indicated, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has improved to ≤ Grade 2 resume study drug (decrease one dose level) • Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has not improved to < Grade 3, permanently discontinue and follow for PD
Grade 4 OR if dialysis is indicated	• Permanently discontinue and follow for PD
Liver function abnormalities	• In case of ALT > 3.0 and ≤ 5.0 x ULN and total serum bilirubin ≤ 1,5 x ULN continue current dose level and test again at next scheduled visit • In case of either ALT > 5,0 x ULN or total serum bilirubin > 1,5 x ULN interrupt lenalidomide therapy. Evaluate ALT and total serum bilirubin weekly until both return to baseline levels. Resume lenalidomide when ALT and bilirubin return to baseline. Maintain dose level if recovery from event occurs ≤ 14 days from initial test result. Decrease by one dose level if recovery from event is prolonged > 14 days but ≤ 28 days from initial test result. • Continue to monitor weekly LFTs during this cycle. If the event does not repeat, dose escalation or re-escalation may continue according to protocol. • **Notify GCLLSG if values do not return to baseline within 28 days of the initial event.**
Cairo-Bishop Toxicity Grade	
Clinical TLS ≥ Grade 2	• Interrupt lenalidomide therapy. • May resume lenalidomide when the TLS resolves to < Grade 1 (decrease one dose level)

NCI CTCAE Toxicity Grade	Action
Other lenalidomide-related non-hematologic AEs ≥ Grade 3	• Interrupt lenalidomide therapy. • May resume lenalidomide when the adverse event resolves to ≤ Grade 2 (decrease one dose level or maintain dose level per the investigator's discretion)

Subjects will receive study maintenance therapy until PD develops[1].

All possible efforts should be made to continue to follow subjects who discontinue maintenance therapy early (due to reasons other than PD, including unacceptable toxicity, or a second line CLL therapeutic regimen) until PD; for those subjects study visits and serial measurements of efficacy will continue to be performed every 3 months, however some safety evaluations, thyroid function tests, pregnancy tests, the recording of concomitant medication will no longer be done (however, AEs will be reported until 28 days after last dose of the study drug: AEs of special interest, Secondary Malignancies and all SAEs related or unrelated to study procedures or maintenance therapy will continue to be recorded up to end of study;).

Subjects who develop PD including disease transformation (Richter's syndrome or prolymphocytic leukemia), will be discontinued from the study treatment and will be contacted every 3 months until the end of the study for survival, observation for second primary malignancy, subsequent CLL therapies and hospitalizations.

4.10.2. Prophylaxis and early detection of liver damage

In December 2012, Celgene issued a letter informing about a possible risk of severe liver damage in patients treated with lenalidomide in combination with dexamethasone for multiple myeloma. Cases with acute liver failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis and mixed cytolytic/cholestatic hepatitis some of which were deadly were reported. Until December 2011 0,67% of the patients treated with lenalidomide for multiple myeloma experienced any form of liver disease. The reporting rate for liver insufficiency, fibrosis, cirrhosis, cholestasis, jaundice and non-infectious hepatitis were low. In the majority of the fatal cases the patients suffered from advanced malignant disease, had a known active or old liver disease or had many concomitant diseases. So far the mechanism and the pathophysiology are unknown but a possible relationship between lenalidomide and the reported liver diseases cannot be excluded. Possible risk factors include the history of viral hepatitis, existing elevated liver enzymes and treatment with antibiotics.

As lenalidomide is excreted through the kidneys it is extremely important to assess the kidney function on a regular basis to prevent high plasma levels. The concomitant administration of lenalidomide, a PGP (P-glycoprotein)/ MDR (multi drug resistance protein) – substrate, together with PGP-inhibitors might lead to increased plasma levels and therefore to increased toxicity. PGP inhibitors include Clarithromycin, Itraconazol, Ketoconazol, Verapamil, Cyclosporin, Quinidin. Whenever possible, none of the medications listed above should be used. Otherwise the patient needs to be monitored very closely. Furthermore regular liver function tests (AST/ ALT/ bilirubin) at least right before every new cycle are mandatory in order to recognize any liver damage as early as possible. Drugs with the potential to damage the liver should be avoided whenever possible. Paracetamol should not

be used as routine pain medication if NSAIDs are well tolerated and not contraindicated in the patient. When treatment with antibiotics is needed the patient is to be monitored for any sign of liver damage. AST, ALT and bilirubin have to be tested prior to start of antibiotic treatment and weekly while under treatment.

Overview:

- Serum creatinine at day 0/1 of each cycle, right before treatment with antibiotics and weekly while under treatment with antibiotics
- Total bilirubin, AST and ALT at day 0/1 of each cycle, right before treatment with antibiotics and weekly while under treatment with antibiotics
- Whenever possible, do not use drugs which are potentially hepatotoxic
- Avoid using paracetamol and do use NSADs instead whenever possible. Do inform your patient about the maximum daily dose of paracetamol
- Avoid using Clarithromycin, Itraconazol, Ketoconazol, Verapamil, Cyclosporin, Quinidin whenever possible
- If Clarithromycin, Itraconazol, Ketoconazol, Verapamil, Cyclosporin or Quinidin is indicated lenalidomide has to be paused for that period. Total bilirubin, AST and ALT have to be tested prior to start with the drugs listed above and while under treatment.

For the actions that need to be taken in case of elevated liver enzymes/ creatinine, please refer to Table 5 Dose Reduction and Modification Guidelines

4.10.3. Description of investigational medicinal product

Lenalidomide (REVLIMID®; Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs®). It offers potential benefit over the first commercially available IMiD, thalidomide, in terms of both safety and efficacy in human subjects[65,66] . The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T-cell costimulatory, and antiangiogenic activities[65].

REVLIMID® has been approved by multiple global Health Authorities (including the FDA and EMA) for the treatment of subjects with transfusion dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndrome associated with a deletion 5q cytogenetics abnormality with or without other cytogenetic abnormalities.

REVLIMID® has also been approved by multiple global Health Authorities (notably including the FDA and EMA) in combination with dexamethasone, for subjects with previously treated multiple myeloma.

Lenalidomide is being investigated as treatment for various oncologic indications, including multiple myeloma, non-Hodgkin's lymphomas, and solid tumors. While many of the studies are ongoing, results from controlled and uncontrolled studies in subjects with MDS and MM are available.

4.10.3.1. Manufacture and packaging of the study drug

Lenalidomide will be supplied in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration labeled as investigational product in HDPE child resistant bottles.

Study drug will be packaged in bottles containing study capsules for 28 days. Those subjects de-escalated to lenalidomide 2.5 mg every other day will receive 14 days of active drug with 2.5 mg capsules. Subjects requiring dose reduction within a treatment cycle must return the empty bottles or any unused drug and a new bottle will be dispensed. If dose reduction occurs within a cycle, subjects will be given a new 28-day supply and should only take the new drug for the remaining days of the current cycle (i.e. if reduction occurs on cycle day 16, then the subject will take study drug for the remaining 12 days of the cycle).

Please document every treatment modification (treatment discontinuation/treatment reduction) during the 28-day cycle on the CRF. After 28 days, the next cycle starts with the first day of treatment.

4.10.3.2. Labeling of investigational medicinal product

Labeling will be done according to GMP Annex 13. The label for investigational product will bear Sponsor's name and address, the protocol number, EudraCT number, product name, dosage form and strength, lot number, medication identification/kit number, dosing instructions, storage conditions, and quantity of investigational product contained, expiration date, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed or applicable. The study drug should be stored as directed on the respective package labels.

4.10.3.3. Dosage regimen

Subjects will be randomized (2:1) via IVRS/IWRS to receive the following:

- Oral lenalidomide 5 mg daily on days 1-28 of the first 28 day cycle
- If the 5 mg dose level is tolerated lenalidomide should be escalated starting with the second cycle up to the sixth cycle to 10 mg daily on days 1-28 of a 28 day cycle.
- Subjects who are tolerating the 10 mg dose level should be escalated starting with the seventh cycle up to the 12th cycle to 15 mg daily on days 1-28 of a 28 day cycle
- Subjects who are tolerating the 15 mg dose level and have not achieved an MRD-level < 10^{-4} in the peripheral blood may be escalated starting with the 13th up to the 18th cycle to 20 mg daily on days 1 through 28 of each 28-day cycle up to disease progression.
- Subjects who are tolerating the 20 mg dose level and have not achieved an MRD-level < 10^{-4} in the peripheral blood may be escalated starting with the 19th cycle to 25 mg daily on days 1 through 28 of each 28-day cycle up to disease progression

4.10.3.4. Order and storage of investigational medicinal product

The study drug ordering will be accomplished via the GCLLSG team though the IDOS system. IDOS is a web-based drug ordering system. Site personnel must complete a drug order form and sent it via Fax to the GCLLSG (+49 (0)221 478 86886).

The Investigator is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order form. The Investigator will verify the accuracy of the information on the form and confirm receipt of shipments to the GCLLSG team. The GCLLSG then will register receipt in IDOS.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. All study drugs (lenalidomide and allopurinol) should be stored as directed on the respective package labels.

FCBP (This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months) should not handle or administer study drug unless they are wearing gloves. All subjects and their caregivers should not extensively handle or open study drug capsules and should maintain storage of capsules in the packaging until ingestion.

Study drug will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by the sponsor in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to study drug being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed lenalidomide Education and Counseling Guidance Document (Appendix 11.18), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was preformed and results were negative. A lenalidomide Information Sheet (Appendix 11.19) will be supplied with each study drug dispense.

4.10.4. Study drug Accountability

The Investigator(s) or designee(s) is responsible for accounting for all study drugs that is issued to and returned by the subject during the course of the study.

The sponsor will instruct the Investigator(s) on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the subject's CRF and source documents. The sponsor will provide instructions for the return of study drug supplies at the end of the study.

4.10.5. Assignment of trial subjects to treatment groups

For this trial, study subjects, investigators, staff, and sponsor‘s clinical and medical representatives were blinded to the treatment assignments.

Randomization, drug dispensing, dose reduction/escalation, and drug discontinuation were accomplished by an IVR/IWR system. Authorized site personnel had to contact the IVRS/IWRS for randomization, study drug assignment at the beginning of each cycle, to register dose reductions or escalations, and treatment discontinuation.

Recruitment as well as randomization was stopped by end of March 2016 and after approval of amendment 5 the patients will be centrally unblinded. The IVRS/IWRS will not be used anymore and drug order will be accomplished via the GCLLSG team though the IDOS system.

4.10.6. Blinding and Unblinding

For this trial, study subjects, investigators, staff, and the sponsor‘s clinical and medical representatives will all be blinded to the treatment assignments. Both study medication and placebo capsules are identical in appearance. The blind must not be broken during the course of the study unless in the opinion of the Investigator it is absolutely needed to safely treat the subject. Every effort should be made to contact the Study Office of the German CLL Study Group in Cologne (Tel: +49-(0)221-478-88220 or e-mail: cllstudie@uk-koeln.de) prior to breaking the blind. Unblinding can be accomplished 24 hours/day via the IVRS/IWRS; authorized site staff may contact the IVRS/IWRS to obtain the subjects treatment arm information. The reason for breaking the blind must be documented in the subject’s case report form (CRF) and in the subject’s medical records. Documentation of contact or attempted contact with the clinical research physician of the GCLLSG central study office prior to breaking the blind must also be documented in the subject’s medical records.

The first interim analysis was performed on a data set with data cut-off date 31st March 2016. At the same time the randomization was closed. The results of the interim analysis were statistically significant, robust and reliable. The DSMB therefore recommended to unblind the patients and to further observe the patients in the placebo arm and to continue with the treatment in the lenalidomide arm.

After approval of amendment 5 the patients will be centrally unblinded, sites will be notified about the unblinding with a written confirmation.

4.10.7. Previous and concomitant medication

Prophylaxis for TLS, thromboembolism and infection and treatment of tumor flare reaction (TFR)

In subjects with bulky disease (at least one lymph node >5cm in the largest diameter) TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at each dose level. Subjects with bulky disease and a known allergy to allopurinol will be excluded from the study. Allopurinol should be permanently discontinued for any adverse reaction deemed possibly related to allopurinol administration. For a Grade 1 or 2 rash, allopurinol should be discontinued prior to study drug to try to determine causality. If the rash does not improve, the study drug should be adjusted per the investigator’s discretion. For a Grade 3 or 4 rash, allopurinol should be discontinued and study drug adjusted as outlined in Table 5. In the event of development of renal impairment, allopurinol should be discontinued and study drug adjusted as outlined in Table 5.

If a subject is taking allopurinol for a condition other than for TLS prophylaxis, the subject should be continued on the allopurinol prescribed by their physician and the dose titrated to 300 mg / day. If, at any time, the allopurinol being taken for reasons other than TLS prophylaxis is discontinued and prophylaxis is still required per protocol, the subject should be administered allopurinol.

Investigators should ensure that their subjects remain well hydrated during the treatment period; this is particularly important during the first 2 cycles of treatment. Subjects should be monitored frequently for development of metabolic changes, and additional chemistries may be performed at the investigator’s discretion, particularly for those subjects who enter the study with still marked lymphadenopathies and/or organ involvement. To maintain fluid

intake, subjects must be instructed to drink 8 to 10 eight ounce (240 mL) glasses of water each day for the first 14 days of cycle 1 and the first cycle of each dose escalation. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload.

Grade 1 TFR may be treated with NSAIDs (i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed) and TFR ≥ Grade 2 should be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Subjects will be monitored for TLS and TFR on Days 1, 8 and 15 for cycle 1 and the first cycle of each dose escalation. Monitoring for TLS and TFR will continue as clinically indicated.

Subjects should be closely monitored for evidence of arterial and venous thromboembolic events while on study drug. Modifiable risk factors for thromboembolic events should be managed wherever possible (eg, smoking cessation; control of hypertension and hyperlipidaemia). Medicines that may increase the risk of thromboembolism, such as oestrogens and erythropoietic agents, should be used with caution during lenalidomide treatment. In case of hospitalization the subject should receive appropriate antithrombotic medication during the duration of the hospitalization. The investigator may use appropriate anti-coagulation prophylactic therapies (i.e. LMW heparin, fondaparinux, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (i.e. subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history). In case of contraindications for prophylactic anti-coagulation medication, compression stockings are recommended. Subjects with no history of DVT or arterial thromboembolic events within the past 12 months, no clear indication or contraindication for antiplatelet or anticoagulant therapy, with no active bleeding, and who are not considered to be at high risk of bleeding should receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug..

Aspirin should be interrupted if the platelet count drops below 50,000/µL.

Prophylactic antibiotics should be considered in subjects with neutropenia. Subjects with an active infection requiring systemic antibiotics and subjects with a systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy are excluded from entering the study.

Treatment and Dose Modification for Tumor Lysis Syndrome (TLS)

Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop definition and grading system should be treated as follows:

- Subjects must be hospitalized for ≥ Grade 1 TLS. For laboratory TLS, hospitalization is left to the investigator's discretion.
- The following should be provided: vigorous hydration and appropriate therapy (i.e. rasburicase where available) as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Dose escalation to the next consecutive dose level will be permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.
- Subjects with ≥ Grade 2 TLS will have their dose interrupted and will resume lenalidomide at the next lower dose when electrolyte abnormalities are corrected (i.e.

Grade 0) as specified in the Dose Modification and Interruption section of the protocol. If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.

- When those subjects that have been dose reduced complete two full cycles without meeting criteria for laboratory TLS or ≥ Grade 1 TLS or experiencing toxicities, re-escalation to their maximum dose level or to the next higher dose level is permitted.

All medications (prescription and non-prescription) including birth control methods, treatments and therapies taken from 30 days prior to the start of study drug through the last dose of study drug, must be recorded on the appropriate page of the CRF. Subjects will be monitored for tumor lysis syndrome and tumor flare reaction early in the treatment.
Tumor lysis syndrome and tumor flare reaction will be recorded as AEs. Non-steroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics or prednisone may be used to treat tumor flare reaction. Aspirin should be interrupted if the platelet count drops below 50,000/ μ L. If a subject develops a VTE during the study, the subject should be treated at the investigator's discretion with an anti-coagulant. If a subject develops a VTE during the study, the subject should be treated at the investigator's discretion with an anti-coagulant. It is recommended to utilize myeloid and erythroid growth factors as per the ASCO guidelines. The use of myeloid growth factors is encouraged when the ANC is < 1,000/µL. Other therapies considered necessary for the subject's well being may be administered at the discretion of the Investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications as well as growth factors and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with chronic lymphocytic leukemia or its therapy. Descriptions of permitted previous and concomitant therapies are decribed in section 4.10.8 and 4.10.9 respectively.

4.10.8. Prohibited medication

Use of other CLL therapies or experimental therapies during screening and while the subject is on study drug is prohibited.

4.10.9. Continuation of treatment after the end of the clinical trial

Trial subjects who do not develop progression of disease during the conduct of the trial and wish to continue with the study drug after end of study are allowed to be treated after the end of the trial up to progression of disease. Lenalidomide will be provided through the subject access program. Such subjects will be reconsented to continue on lenalidomide.

4.11. Efficacy and safety variables

4.11.1. Measurement of efficacy and safety variables

4.11.1.1. Primary target variable

Efficacy:

- Lymph nodes, spleen and liver measurements by physical examination

- Complete blood count (CBC)
- Peripheral blood smear
- Flow cytometry of peripheral blood for MRD assessment
- Bone marrow aspirate/biopsy for standard histopathology and flow cytometry for MRD assessment
- Computed tomography (CT) scans if clinically indicated
- ECOG Performance Status
- Assessment of constitutional symptoms

4.11.1.2. Progressive disease

Progressive disease is characterized by at least one of the following[1]:

- Lymphadenopathy. Progression of lymphadenopathy discovered by physical examination. Disease progression occurs if one of the following events is observed:
    - Appearance of any new palpable lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
    - An increase by 50% or more in greatest determined diameter of any previous site.
    - An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per µL.
- Transformation to a more aggressive histology (e.g. Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL
- During therapy: cytopenias may occur as a side effect of many therapies and should be assessed. During therapy, cytopenias cannot be used to define disease progression.
- Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/µL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

4.11.1.3. Safety analysis

Safety:

- Vital signs: pulse, blood pressure, temperature, and weight
- Clinical laboratory evaluations:

- Hematology: white blood cell (WBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), differential, platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), prolymphocytes and reticulocyte count
- Chemistry: calculated (method of Cockroft-Gault) creatinine clearance (screening only), sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid
- Thyroid functions: TSH, T3 and T4

- Pregnancy testing for female subjects with childbearing potential: serum or urine pregnancy testing (β-HCG) with a sensitivity of at least 25 mIU/mL is to be done on FCBP only
  - FCBP should be monitored during the course of the study and after the end of study therapy to:
    - Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (see specifics in Appendix 11.18)
    - Ensure the subject continues to practice abstinence or remains on adequate contraception (see specifics in Appendix 11.20.)
    - If a FCBP becomes pregnant treatment should be stopped and the subject referred to the appropriate physician
- Male subjects should be monitored during the course of the study and 28 days after the end of study therapy to:
  - Ensure they commit to continued abstinence from heterosexual contact or continue to use a condom during sexual contact with a FCBP
  - If a female partner of a male subject becomes pregnant she should be referred to an appropriate physician
- ECGs (performed and interpreted locally)
- Concomitant medications
- AEs by NCI CTCAE Version 4.0 with modifications recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia[1]
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study drug, occurring at any time for the duration of the study, from day 1 of the first cycle up to and including the survival follow up phase.
- Quality of Life will be measured by EORTC QLQC30 and EQ-5D.

4.11.1.4. Exploratory

Only in patients who underwent pre-screening procedures before activation of amendment 3.

Exploratory:

- FISH analyses, ZAP 70, mutational status assessment, quantitative immunoglobulins assessment and flow cytometry (MRD)
- Thymidine kinase, Beta-2 Microglobulin (β2M)
- Genetic or biological markers of predictive value with regard to study endpoints

4.11.1.5. Health Economics

Quality of Life information based on EORTC QLQ-C30 and EQ-5D questionnaires will be recorded because it may provide valuable information on the utility and cost (in terms of quality of life)/benefit of maintenance therapy.

The EORTC QLQ-C30 will be administered as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/QOL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all, ""A little," "Quite a bit" and "Very much." The two items assessing global health status/QOL utilize a 7-point scale ranging from 1 (“Very Poor”) to 7 (“Excellent”).

All of the scales and single item measures range in score from 0-100. A high score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QOL represents a high/good QOL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

EORTC QOL module for chronic lymphocytic leukemia: EORTC QLQ-CLL16

This module is designed for subjects with stage 0 to stage 4 chronic lymphocytic leukemia. It is comprised of sixteen questions that address five domains of HRQoL important in CLL. There are three multi item scales on: Fatigue (2 items), treatment side effects and disease symptoms (8 items), infection (4 items) and two single item scales on social activities and future health worries

The EQ 5D EQ-5D™ is a standardised instrument for use as a measure of health outcome, it provides a simple descriptive profile and a single index value for health status. EQ-5D is designed for self-completion by subjects. It is cognitively simple, taking only a few minutes to complete. Instructions to subjects are included in the questionnaire.

4.12. Methods and Timing of Efficacy Assessments

Serial measurements of efficacy will be performed at screening and at scheduled intervals throughout the duration of the study as outlined in Table 2 Study Assessment Plan: Visit schedule**.** All scheduled visits will have a ± 7 day window unless otherwise stated.

Peripheral blood for MRD status will be drawn at pre-screening and at screening for all subjects entering and repeated after 6 cycles, 12 cycles, 18 cycles, 24 cycles and then annually (36, 48 and 60 months). Bone marrow aspirate and biopsy will be performed for all subjects at screening; if this bone marrow is hypocellular, a repeat specimen including adequate biopsy sample should be obtained 4 weeks later. At screening a bone marrow aspirate will also be used for confirmation of the response achieved after first line treatment and additionally to assess MRD levels and to compare the results with the MRD levels observed in the peripheral blood.

CT scans of the chest, abdomen and pelvis will be performed at screening for all subjects. If clinically indicated CTs might be repeated after 12 cycles of treatment and at disease progression at the discretion of the investigator.

ECOG Performance Status and evaluation of constitutional symptoms to be measured during screening, on Day 1, every 28 days and at the treatment discontinuation visit.

4.13. Methods and Timing of Safety Assessments

Serial measurements of safety will be performed at screening and at scheduled intervals throughout the duration of the study as outlined in Table 2 Study Assessment Plan: Visit schedule. All scheduled visits will have a ± 7 day window unless otherwise stated. Abnormalities will be captured as adverse events. The adverse event of flare reaction, which may mimic disease progression, may render the efficacy assessments not evaluable at the corresponding visit(s). Lab abnormalities are only considered AE if they fulfill one of the following criteria:

- accompanied by clinical symptoms
- leading to a change in study medication (e.g. dose reduction, interruption or permanent discontinuation)
- requires a change in concomitant therapy (e.g. addition or change in a concomitant medication, therapy or treatment)

All Grade 4 laboratory abnormalities fulfilling the criteria for an SAE will be reported to GCLLSG Study Office as SAEs and will be recorded on the AE pages of the CRF, however those that are not deemed by the investigator to be part of a diagnosis or syndrome will not be reported to the Health Authorities in an expedited manner. Lymphopenia is an expected and desired effect of therapy and so should not be reported as an adverse event or serious adverse event. Cause of death is to be recorded in the CRF and the subject's medical record.

4.14. Assessment of Other Outcomes

- FISH analyses
- CD38/ZAP 70

- Mutational status analysis
- Immunophenotyping by FACS
- Minimal residual disease levels by flow cytometry
- Serum-β2microglobulin and serum thymidine kinase

4.15. Methods and Timing of Other Outcomes

Only for patients who underwent pre-screening procedures before activation of amendment 3: Peripheral blood samples for immunophenotyping by FACS, FISH analysis and MRD baseline sample will be obtained during pre-screening and forwarded to a central laboratory. Prognostic panel including 11q, 17p, 13q, trisomy 12 and *TP53* mutational status, will be utilized to identify and characterize chromosomal and genetic abnormalities in the study population. Blood samples for FISH, ZAP 70, *IGHV* mutational status and serum samples for the analysis of β2microglobulin and serum thymidine kinase will be forwarded to a central lab and analyzed.

MRD will be quantified by four-color flow cytometry with a sensitivity of at least 10^{-4} according to the technique previously described and validated against ASO-primer real-time quantitative IGH-PCR[34]. The method utilizes an international standardized approach[35] with minor modifications on subject samples received within 48 hours after collection. MRD analyses will be repeated as outlined in section 4.12. The relationship between progression free survival, overall survival, response rates and cytogenetic abnormalities will be explored.

Peripheral blood samples for quantitative immunoglobulins assays will be obtained during maintenance therapy to assess immune reconstitution.

Peripheral blood samples for immune cells (NK and T cells) analyses will be collected and analyzed during Pre-screening (only for patients who underwent pre-screening procedures before activation of amendment 3), screening and after 6 months and one year of treatment.

4.16. Data quality assurance

4.16.1. Monitoring

Monitoring will be performed by the Competence Net Malignant Lymphoma (KML) for the German and Austrian sites.

Monitoring outside of Germany and Austria will be conducted by monitors of academic research organizations or clinical research organizations according to the agreement with the sponsor's representative of the respective country and according the global monitoring plan and manual.

The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the Case Report Form. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when Case Report Forms are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The exact extent of the monitoring procedures is described in a separate monitoring manual including instructions for each site initiation visit, selection visit for inexperienced sites and close-out visits.

All investigators agree that the monitor regularly visits the trial site and assures that the monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The declaration of informed consent (see Section 5.3) includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the case report forms (CRFs) with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs)
- To check the completeness and accuracy of entries on the CRFs
- To validate the entries on the CRFs against those in the source documents (source data verification, SDV)
- To perform drug accountability checks
- To evaluate the progress of the trial
- To evaluate compliance with the trial protocol
- To assess whether the trial is being performed according to GCP at the trial site
- To discuss with the investigator aspects of trial conduct and any deficiencies found

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation).

4.16.2. Audits/Inspections

In addition to the routine monitoring procedures, in this trial audits will be performed by auditors of the Center for Clinical Trials (ZKS) at the University of Cologne on behalf of the sponsor. Selected sites will be audited and ZKS-auditors will conduct audits of clinical

research activities in accordance with ICH/GCP to evaluate compliance with Good Clinical Practice guidelines and regulations. All persons conducting audits undertake to keep all trial subject data and other trial data confidential. The Investigator(s) is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g. FDA, EMA) and sponsor's authorized representatives. The Investigator(s) should make every effort to be available for the audits and/or inspections. If the Investigator(s) is contacted by any regulatory authority regarding an inspection, he/she should contact the Central Study office of the GCLLSG immediately.

4.17. Documentation

All subject-related data will be recorded in a pseudonomized way. Each subject will be unequivocally identified by a trial subject number, attributed at recruitment into the study. The investigator is required to keep a subject identification log, including the full name and address of the subject and eventually additional relevant personal data such as hospital record number, home physician etc.

All the data retrieved during the conduct of the study are to be entered into the appropriate case report forms (CRF) by the investigator or another person authorized by the investigator. The CRFs will be provided by the study office and explained to the investigators/documentation personnel during an investigator meeting, a study group meeting or by a monitor during the initiation visit.

All recorded data are to be plausible and complete. The following technical instructions are to be adhered to when the CRFs are used:

- Use black or blue ballpoint pens only in order to insure that all copies are legible.
- Write only one letter or numeral in each of the open boxes of the data fields. Closed boxes are to be crossed only ("check-boxes").
- All data fields have to be filled, except for those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done= ND, not applicable, not available = NA, unknown= UK).
- If a date is not known exactly, please fill in the respective field according to the following example: – – 08 12, meaning unknown day in August 2012.
- If any corrections have to be performed in the CRF by the investigator or co-investigator, they have to be performed according to GCP principles, i.e. the original entry has to be crossed out (i.e., with a single line through) while remaining legible. The correct information is then written legibly beside or above the original one. The correction (or addition) is to be dated and signed or initialed.
- Please write legibly and use block letters.

The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data. The completed forms are signed by the investigator, where necessary. The original has to be sent to the GCLLSG-Data management office. A copy remains with the investigator. The study office or monitor checks the forms for completeness

and plausibility. If queries are raised during the data cleaning process, query forms will be sent to the investigator for clarification, who will correct or complete as required and send the signed query form back to the GCLLSG Study office.

All data entered on the CRF must be documented in a source document. The CRF is not a source document. The subject will be asked to record data in the Quality of Life Questionnaire according to the instructions given for that data collection tool.

All protocol required procedures along with information necessary to report the observations and tests described in this protocol will be recorded in the CRFs. CRFs must be completed and send to the GCLLSG Study Office in a timely and accurate manner by site personnel. Monitors are allowed to collect completed CRFs at the sites during the monitor visits and should deliver the collected CRFs to the GCLLSG study office within one week after collection.

CT scans must be reported in summary in the CRF. The original reports, traces and films must be retained by the investigator for future reference.

The investigator must review all pages within the CRF for accuracy and consistency with the protocol, and sign and date the CRF sign-off page(s) upon completion.

All CRFs must be completed in black or blue ink. Corrections to data on the CRFs must be made by lining out the incorrect data with a single line and writing the correct data near to those crossed out. Correction fluid is not to be used to cover errors. Each correction must be initialed (or signed) and dated by the person making the correction.

4.17.1. Data management

The Central Study Office of the GCLLSG is responsible for the IT infrastructure and data management staff. The Clinical Data Management System and technical support will be provided by the Systems R&D, Clinical Trials Unit Cologne, a joint software development group which is part of the Cologne Clinical Trials Unit and the Department 1 for Internal Medicine (Prof. O. A. Cornely, Prof. M. Hallek). The data management system is developed according FDA Title 21 CRF Part 11 and Guidance for Industry Computerized Systems Used in Clinical Investigations and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The clinical data management system will be integrated into a general IT infrastructure and safety concept with a firewall and backup system. After completion and cleaning of data, the database will be locked for final export with the purpose of statistical analyses. The trial database will be tested before data entry according to standard operating procedures of Systems R&D and the GCLLSG.

We will follow an established procedure whereby the arrival of CRFs at the Central Study Office of the GCLLSG is documented and the data is checked for completeness. Independent data entry staff enters the data into the clinical data management system. For verification and to detect data entry errors the data entered is reviewed by the data managers. Plausibility checks are also conducted in the system. Discrepancies and implausible values are clarified in writing between the data manager and the trial site. The trial site has to answer these queries without unreasonable delay. Answered queries have to be signed and dated by the investigator. Further details will be specified in the data management plan.

4.17.2. Archiving

All CRFs, informed consent forms and the complete Trial Master File, including other important trial materials will be archived for at least 10 years from the end of the study in accordance with §13 Sec. 10 of the GCP Regulations. Trial subject identification lists at each trial site will be stored separately from trial documentation.

5. Ethical and regulatory aspects

5.1. Ethical considerations

The Sponsor and all investigators agree to conduct this study in accordance with the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP) and with the Declaration of Helsinki (revised version of Somerset West, South Africa, 1996, see Appendix 11.15). The investigators will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

The participating investigators/institutions permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections and provide direct access to source documents/data. The investigator assumes the responsibility of obtaining written informed consent for each subject before any study-specific procedures are performed and before any study drug is administered. If an amendment to the protocol changes the risk participation schedule in scope or activity, or increases the potential risk to the subject, the informed consent document must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment and must be used to document consent from any new subjects enrolled after the approval date of the amendment. The Sponsor and the investigators affirm and uphold the principle of the subjects' right to privacy. The investigators shall comply with applicable privacy laws. The investigator must assure that the subjects' anonymity will be maintained and that the identities are protected from unauthorized parties. The investigator should maintain documents not for submission to the GCLLSG study office e.g. subjects written consent forms, in strict confidence. All clinical and scientific data are collected under a unique code (or "pseudonym" containing of an abbreviation of the study, a meaningless string of 6 digits) and stored in the main clinical trial database. All data exchange with the study center is made solely via the unique code. All participating study centers are obliged to keep a secret subject identification list.

5.2. Good Clinical Practice and regulatory requirements

This study will be conducted in accordance with good clinical practices as described in the ICH E6 Guideline for Good Clinical Practice, adopted 1 May 1996. The guideline may be obtained at URL: http://www.fda.gov/cder/guidance/959fnl.pdf or URL: http://www.ich.org.

Furthermore the study will be performed in compliance with the EU Directive on clinical trials 2001/20/EC and the the EU Directive on Good Clinical Practice 2005/28/EC. In Germany, the requirements according to the following documents will be fulfilled: Deutsches Arzneimittelgesetz (AMG, geändert durch Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 19.10.2012) and "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen" from August 9th. 2004 (GCP-V, geändert durch Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 19.10.2012).

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The Sponsor will be responsible for

preparing documents for submission to the relevant ECs as well as the Clinical Trial Application to the appropriate Health Authorities and obtaining written approval of both the EC and the appropriate Health Authorities for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number. Any amendments to the protocol after receipt of EC/BfArM approval must be submitted by the Sponsor to the EC as well as the appropriate Health Authorities for approval. The Sponsor is also responsible for notifying the EC as well as the BfArM of any serious deviations from the protocol, or anything else that may involve added risk to subjects. Any advertisements used to recruit subjects for the study must be reviewed and approved by the EC prior to use. The participating investigators/institutions permit trial-related monitoring, audits, IEC review, and regulatory inspections and provide direct access to source documents/data.

5.3. Obtaining informed consent from trial subjects

The investigator assumes the responsibility of obtaining written informed consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed and before any study drug is administered. Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper informed consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate. Documentation that informed consent documented by the use of a written consent form that includes all the elements required by regulations and ICH guidelines occurred prior to the subject's entry into the study and of the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the subject. The date and time of the informed consent must additionally be recorded in the source documents In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the subjects subjects enrolled after the approval date of the amendment, the original amended consent form signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's study files and a copy given to the subject.

Trial subjects may not be enrolled into the present trial unless they have consented to take part in the trial after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences by a trial investigator. Together with the consent to take part in the trial, the trial subject must also agree to representatives of the sponsor (e.g. monitors or auditors) or the competent supervisory or federal authorities having access to the data recorded within the framework of the clinical trial. The trial subject will be

informed of the potential benefit and possible side effects of the Investigational Medicine Product (IMP) and placebo, and of the need and reasons to conduct a placebo-controlled clinical trials. It must be clear to trial subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment.

The subject information sheet and informed consent form are supplied in Appendix 11.5.

The subject information sheet, informed consent form, all other documents handed out to the trial subject and any recruitment advertisements must be submitted for approval before use to the ethics committee. Part of the monitoring activities are to check that the most recent informed consent form was used before the trial subject was enrolled and that it was dated and signed by the trial subject himself or herself.

5.4. Insurance of trial subjects

All trial subjects enrolled are insured in accordance with § 40 AMG, details for the german insurance are to be found on 11.9. The headquarters, policy number and telephone and fax number of the respective insurance company of each country will be included in the subject information sheet.

5.5. Data protection

The investigator affirms and upholds the principle of the subject's right to privacy. The investigators shall comply with applicable privacy laws. The investigator must assure that the subject’s anonymity will be maintained and that the identities are protected from unauthorized parties. Should direct access to medical records require a waiver or authorization separate from the subject’s statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing. Trial subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial. The investigator should maintain documents not for submission to the GCLLSG study office in strict confidence. On CRF’s and other documents subjects should not be identified by their names. All clinical and scientific data are collected under a unique identification code for each subject, and stored in the main clinical trial database. Information about the treating centers is stored in a second separate and secret data file linked to the centre code. By keeping the information separately from the main clinical trial database, it is ensured that one cannot draw any conclusions about the identity of the treated individual.

Central laboratory samples arriving from GCLLSG trial sites are labeled with the subject’s unique identification code. All data exchange with the study centre is made solely via the

unique identification code. All participating study centers are obliged to keep a secret subject identification list.

6. Statistical methods and sample size calculation

6.1. Statistical and analytical plan

6.1.1. Trial populations

The primary analysis population for efficacy is the intent–to-treat population defined as all subjects being randomized. Subjects will be assigned to treatment groups as randomized. In addition, a per-protocol population (PPS per protocol set) will be defined for a sensitivity analysis of PFS. This per-protocol population will comprise all subjects who have completed study therapy (defined as having received at least two complete cycles of study therapy) unless progressed or died before, provided they fulfill the inclusion criteria and have no major protocol violations. Subjects are assigned to treatment groups as treated. The purpose of the per-protocol analysis is to assess the robustness of the primary analysis (based on the intent-to-treat population) and to quantify more precisely the magnitude of the potential clinical benefit of the treatment in the target population.

Subjects showing any of the protocol violations listed below will be excluded from the per protocol analysis:

- unconfirmed diagnosis of CLL by NCI working group criteria
- less than 2 cycles of randomized treatment (except for early progression or death)
- inadequate tumor assessment at screening
- no screening assessments of lymphocyte count
- previous treatment of CLL by chemo-, radio- or immunotherapy other than the protocol specified first-line therapy

All safety parameters will be analyzed on the safety population. This population includes all subjects who have received at least one dose of trial treatment, whether withdrawn prematurely or not. The safety parameters will be presented according to the therapy the subject received.

6.1.2. Primary endpoint

Progression-free survival (PFS) based on independent review committee

The primary efficacy parameter is progression-free survival. The time to disease progression will be measured from the date of randomization to the date of first documented disease progression (as defined by the iWCLL response criteria, see section 4.11.1.2) or death by any cause, whichever occurs first. Start of a new CLL treatment after the randomized treatment will not be counted as an event. In all subjects (even if on a new CLL treatment) response has to be assessed until first progression. Patients who have not experienced documented disease progression or death will be censored at the last tumor assessment.

6.1.3. Analysis of the primary endpoint

This analysis will be performed on the ITT-population.

The primary objective of the study is to compare the following hypothesis:

Progression free survival of Lenalidomide versus Placebo i.e.

H0: Lenalidomide = Placebo versus H1: Lenalidomide ≠ Placebo

The two treatment arms will be compared for progression-free survival by using a two-sided log-rank test. In addition Kaplan-Meier estimates, median time of progression-free survival as well as progression-free survival rates for one, two and three years after randomization with 95% confidence intervals will be reported.

Two formal interim analyses have been subsequently planned when 20% (24 events) and 41% (48 events) of the total 118 PFS events have been observed. PFS will be tested at the significance level determined using the Hwang-Shih-DeCani spending function with parameter $\gamma = -2$ for the lower futility boundary and the Hwang-Shih-DeCani spending function with parameter $\gamma = -4$ for the upper efficacy boundary. The significance level will be adjusted to incorporate the α-spent at the interim analyses, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

6.1.4. Secondary endpoints for efficacy

Progression-free survival (PFS) based on investigator's assessment

The time to disease progression will be measured from the date of randomization to the date of first disease progression (as defined by the iWCLL response criteria, see section 4.11.1.2) estimated by the independent review committee or death by any cause, whichever occurs first. Start of a new CLL treatment after the randomized treatment will not be counted as an event. Patients who have not experienced documented disease progression or death will be censored at the last tumor assessment.

Progression-free survival based on investigator's assessment censoring subjects who started new anti-leukemic therapy before disease progression

The time to disease progression will be measured from the date of randomization to the date of first documented disease progression (as defined by the iWCLL response criteria, see section 13.4) estimated by the independent review committee or death by any cause, whichever occurs first. Start of a new CLL treatment after the randomized treatment will be counted as a reason for censoring. Patients who have not experienced documented disease progression or death will be censored at the last tumor assessment.

Overall survival (OS)

OS will be calculated from the date of randomization to the date of death due to any cause. Subjects who have not yet died at the time of the final analysis will be censored at the time of the last contact. The exact cause of death will be recorded, with additional differentiation between CLL-related, treatment-related and other causes.

Time to next CLL treatment (TTNT)

The time to new CLL treatment will be calculated from the date of randomization to the date of starting a new CLL treatment. Subjects who have not yet received a new CLL treatment at the time of the analysis will be censored at the time of the last contact.

Event-free survival (EFS)

EFS will be calculated from the date of randomization to the date of progression, the beginning of new treatment for any hematological malignancy or progression of disease or death by any cause, whichever occurs first. Subjects who have not experienced documented disease progression, received new CLL treatment, or died will be censored at the last tumor assessment.

MRD remissions

MRD levels (evaluation of minimal residual disease (MRD) by flow cytometry and comparison between MRD levels immediately after first-line therapy to levels 6 cycles, 12 cycles, 18 cycles, 24 cycles and then annually after treatment with lenalidomide). It is anticipated that some subjects entering the study, randomized to the lenalidomide arm, with the evidence of minimal residual disease will further achieve MRD negativity over the duration of treatment in contrast to the subjects randomized into the placebo arm.

The number of subjects with MRD response (grouped as $< 10^{-4}$, $\geq 10^{-4}$ to $< 10^{-2}$, $\geq 10^{-2}$) in percent of the respective population will be analyzed. It will be summarized, if subjects show improvement from their MRD status after first-line treatment while on study treatment. Rates and 95%-confidence limits will be given for each treatment group.

Quality of life

Quality of life will be determined on the basis of the EORTC quality of life index (EORTC QLQ C30) and the EQ-5D Questionnaire. After examining Cronbach's alpha quality of life will be analyzed using a linear mixed model with scale at respective time as dependent variable and time, scale at screening and treatment arm and their interactions as explanatory variables.

6.1.5. Analyses of secondary endpoints

No adjustment for multiplicity will be done.

A two-sided non-stratified log-rank test of PFS based on the investigator's assessment will be performed on the per protocol population to confirm the primary statistical analysis. A two-sided stratified log-rank test of PFS based on the investigator's assessment with the stratification factor (MRD level will be performed on the ITT-population to confirm the primary statistical analysis.

Time to event endpoints will be analyzed in a similar way as the primary analysis on the ITT-population.

Rates will be compared using a chi-square test or exact-test of Fischer, as appropriate. Rates and 95% confidence limits will be given for each treatment group. The effect of prognostic factors will be assessed in an exploratory analysis using logistic regression with the following covariate (MRD level).

Summary descriptive statistics will be performed for continuous variables.

Multivariate analyses using a Cox regression model adjusted for treatment and baseline prognostic factors will be performed. Variables will be defined and may include but not limited to age, gender, Binet stage, cytogenetics, IGHV mutational status, time from first diagnosis, thymidine kinase, β2-microglobulin, ZAP-70 and CD38.

6.1.6. Safety analyses

Rate of treatment-related adverse effects

The rate of treatment-related adverse events will be determined from the reported side-effects. NCI-CTC criteria version 4 will be used for grading of adverse events and for the analysis of lab abnormalities.

All subjects who receive at least one dose of study medication will be included in the safety analyses.

Adverse events (AE) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.0 whenever possible.

The adverse event of infection will also be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008). AE frequency will be tabulated by body system, MedDRA preferred term for each treatment regimen during the treatment phase as well as for the follow-up phase when appropriate. In the by-subject analysis, a subject having the same event more than once will be counted only once. AEs will be summarized by worst NCI CTCAE version 4.0 grade. In the case that the AEs or event frequencies are judged to be clinically important, an exact test may be used to analyze the difference between the treatment groups.

AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE version 4.0 Grade 3 or higher, study-drug-related events, serious adverse events (SAEs) and events of interest (including second primary malignancies) will be summarized separately. Premature withdrawals due to adverse events will be analyzed.

Laboratory data will be graded according to NCI CTCAE version 4.0 severity grades. Cross tabulations will be provided to summarize frequencies of abnormalities.

For vital sign and body weight data, means, medians, standard deviations, minimum and maximum values will be provided.

Safety variables in this study include adverse events (toxicities assessed using NCI-CTC criteria, Version 4, laboratory values, and physical examination results.

Adverse Events: The NCI CTC Version 4 will be used to assess toxicities observed during the study. Each toxicity observed will be reported as an adverse event, with severity rated in accordance with the NCI-CTC criteria grades. Safety variables will be summarized by percent and two-sided 95%-confidence interval.

Clinical laboratory and hematology variables will be summarized as absolute values and as difference between baseline and end of treatment period values.

6.1.7. Demographic and baseline characteristics

The baseline characteristics will be presented using summary statistics for continuous variables and frequency tables for categorical variables. No formal statistical tests will be applied. Listings and summary tables of standard demographic and baseline disease characteristics will be produced.

6.1.8. Protocol violations

All protocol violations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be summarized and described.

6.1.9. Treatment administration

Treatment administration will be described for all cycles.

Dose administration, delays of more than 7 days and the duration of therapy will be described.

6.2. Sample size calculation

The primary endpoint of PFS was used to determine the sample size for the study.

These following assumptions on the treatment effects were used:

- Median PFS for placebo = 22.4 months
- L-maintenance will improve the median PFS by 75% which will result in a median PFS of 39.2 months

Based on the above assumption a treatment effect of a hazard ratio = 0.571 for L-maintenance versus placebo is implied.

Statistical assumptions for the comparison of L-maintenance versus placebo:

- two-sided Alpha = 5%
- Power = 80%
- Recruitment per month: 12.5 subjects

Then 186 subjects have to be recruited within approximately 16 months and 118 events have to be observed (calculation performed with the package East 5).

Assuming a drop out rate of 7.5% during the study a total number of 200 subjects have to be recruited. Based on the analyses of CLL8 data about 30% of patients after firstline treatment are assessed to be high risk patients. That leads to the number of about 714 patients to be screened.

6.2.1. Subsequent design adjustments

In the course of the study it was realized that the recruitment goal of 200 planned patients might not be reached due to significant lower recruitment rates as planned. Until March 2016, it is assumed to randomize 90 patients approximately. Thus, it would not be possible to

perform the planned final analysis after 118 PFS events, so that the study would not be analyzable at the end of recruitment. Therefore, it was decided to subsequently revise the initial design according to a group sequential design including two interim analyses and one final analysis. Based on interim results, the DSMB will determine a recommendation thus retaining the chance to bring the study to a valid conclusion. Moreover, a revised recruitment rate consisting of two periods (randomization rate = one subject per month for the first year, and two subjects per month thereafter) was taken into account together with the following assumptions and design parameters:

- Log-rank test at the two-sided 0.05 significancy level
- Median PFS for placebo = 22.4 months
- L-maintenance will improve the median PFS by 75% which will result in a median PFS of 39.2 months implying a treatment effect of a hazard ratio = 0.571 for L-maintenance versus placebo
- Power = 80%
- Randomization ratio (L-maintenance/Placebo) = 2
- Two interim analyses for both efficacy and futility (non-binding) after 24 and 48 PFS events, utilizing stopping boundaries according to Hwang-Shih-DeCani spending function with parameters $\gamma = -4$ (alpha-spending function for the upper bound) and $\gamma = -2$ (beta-spending function for the lower bounds).

Based on these assumptions, a total of 118 PFS events are required to being observed in the initially planned 200 patients for the final PFS analysis. Thus, five additional events are required only to account for two formal interim looks in comparison to the intial fixed sample design.

6.3. Interim analyses of the primary endpoint

The cutoffs for the interim analyses will be based on the investigator-assessed PFS events. Both interim analyses were designed to decide whether the study might be stopped early for either efficacy or futility. Futilty boundaries were implemented as non-binding, so that the stop due to futility is not prescribed. Summaries and analyses will be prepared by the independent statistician of the Data Safety Monitoring Board (DSMB) to retain the blinding. Details of the analyses will be described in a separate statistical analysis plan. The first interim analysis will be performed after 24 PFS events of the total 118 PFS events. On the basis of the revised recruitment assumptions as previously described, it is estimated to reach these events in spring 2016 [month 41 approximately]. However, the first interim analysis can be conducted at this time even if the 24 PFS are not reached completely according to the design parameters using spending function approaches. PFS will be tested at the significance level determined using the Hwang-Shih-DeCani spending function with parameter $\gamma = -2$ for the lower futility boundary and the Hwang-Shih-DeCani spending function with parameter $\gamma = -4$ for the upper efficacy boundary. Thus, the upper bound spending computations assume that the study continues if the lower bound is crossed. The second interim analysis is planned after 48 of the total 118 PFS events using the same principles as previously described [month 58 approximately]. The significance level will be

adjusted to incorporate the α-spent at the interim analyses, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

Analyses were performed using R version 3.1.0 (package gsDesign)

Table 6: Definition of boundaries

		Lower boundaries			Upper boundaries		
Analysis	**Events**	**Z**	**Nominal p**	**Spend p**	**Z**	**Nominal p**	**Spend p**
1	24 (20%)	-0.88	0.1889	0.0154	3.25	0.0006	0.0006
2	48 (41%)	-0.08	0.4691	0.0230	2.99	0.0014	0.0013
3	118 (100%)	1.98	0.9760	0.1616	1.98	0.0240	0.0232
Total				**0.2000**			**0.0250**

6.4. Time point of final analysis

The first interim analysis was performed by the independent DSMB statistician on a dataset with data cut-off date 31st March 2016. At this time point 89 patients have been randomized into the study and further randomization was closed. The results of the first interim analysis were statistically significant, robust and reliable with regard to the pre-specified stopping boundaries given by the Hwang-Shih-DeCani spending function (with parameter $\gamma = -2$ for the lower futility boundary parameter $\gamma = -4$ for the upper efficacy boundary). Based on these results, the DSMB concluded that the stopping boundary for efficacy has been surpassed and, as such, recommended to unblind the patients. All patients should be further observed and patients in the lenalidomide arm should continue with the treatment. The further observation of the subjects in the study has the objective to collect further safety data and data for the secondary endpoints.

Concerning future analyses, the second interim analysis will be omitted and the final analysis will be conducted either as soon as all patients have experienced disease progression or at the end of the study (30 days after end of treatment of the last subject, estimated latest in March 2021). The final analysis will be performed in an unblinded fashion by the statistician of the GCLLSG.

7. Safety

Table 7: Reporting periods

Event	Reporting period	Reporting on SAE Form	Documentation on AE/SED page of the CRF
SAE (related and unrelated)	From day 1 of the first cycle during the entire duration of the study	required	required (on AE pages)
Related or unrelated AEs (not fulfilling criteria for an SAE)	From day 1 of the first cycle up to 28 days after the end of the treatment	not required	Required (on AE pages up to 28 days after end of study treatment
AEs of special interest (see section7.1.1) (not fulfilling criteria for an SAE)	From day 1 of the first cycle during the entire duration of the study	not required	Required (on SED and AE pages up to 28 days after end of study treatment, after this time period only on SED page)
Secondary malignancies	From day 1 of the first cycle during the entire duration of the study	required	Required (on AE pages and SED page)

7.1. Definitions of adverse events and adverse drug reactions

7.1.1. Adverse event and Adverse drug reaction

An adverse event (AE) is any untoward medical occurrence after starting study drug treatment, regardless of whether the event is considered related or unrelated to the study drug. An adverse drug reaction (ADR) is any noxious and unintended response to any of the components of the study medication related to any dose with at least a reasonably possible causal relationship with the study medication. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. The investigator will evaluate changes in physical signs, laboratory values, or other diagnostic procedures in determining AEs. Subjective AEs should be elicited by first questioning the subject in a non-directive manner, then, if any unfavorable symptoms are reported, questioning in a more detailed manner to obtain the information necessary for reporting the event. The NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4, will be used for assessing the severity of AEs. A copy of these criteria will be provided in as the appendix 11.14. MedDRA will be used for the coding of adverse events. Pre-existing conditions which worsen during a study are to be reported as AEs.

Lab abnormalities are only considered AE if they fulfill one of the following criteria:

- accompanied by clinical symptoms

- leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- requires a change in concomitant therapy (e.g. addition or change in a concomitant medication, therapy or treatment)

Lymphopenia is an expected and desired effect of therapy and should not be reported as an adverse event or serious adverse event.

AEs of special interest: Infections and auto-immun diseases have to reported during the entire duration of the study. Serious infections and auto-immun diseases have to be reported as SAEs and on the corresponding AE pages. Non-serious infections and auto-immun diseases have to be recorded on AE pages up to 28 days after the end of study treatment and after this time period on the SED pages of the CRF.

Concomitant diseases

Any medical condition that was presented prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome. (see Section 7.1.3*).*

Second primary malignancies

will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from day 1 of the first cycle up to the end of the study (including any follow-up, observation and/or survival follow-up period.) In this study, subjects will be followed for 5 years from randomization of the first patient (or subject died/become lost to follow up before 5 years) or until at least 118 PFS-events have occurred, whichever comes later. Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents (see table in section 7.) Documentation of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results).

Secondary malignancies occurring between signing the ICF and before the start of the study treatment will be considered as exclusion criteria and will be recorded on the CIRS page and should be ticked as exclusion criterion on the prescreening/screening pages.

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an SAE. For details of special reporting requirements for pregnancy, see Section 7.3.

7.1.2. Adverse drug reaction

An adverse drug reaction (ADR) is any noxious and unintended response to an investigational medicinal product (IMP) related to any dose with at least a reasonably possible causal relationship with the IMP.

7.1.3. Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious ADR (SADR) is any untoward medical occurrence that at any dose

1. Results in death
2. Is life-threatening at the time of the event
3. Requires insubject hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly or birth defect (1.-4.: § 3(8) GCP Regulations)
6. Is medically significant in the opinion of the investigator, fullfils any other criteria similar to 1.–4.

In-subject hospitalization is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00). Admission to hospital as an in-subject planned before the first admission of the IMP are not SAEs, but must be documented in the proper manner in the trial subject's medical records and CRF (see Section 7.1.1).

If an AE is classified as an SAE, this is documented on a separate SAE sheet in addition to the standard AE documentation. The authorities must be notified of SAEs by law (for procedure, see 7.3)

Second primary malignancies occurring after subject received the first dose of study drug treatment are classified as SAEs.

7.1.4. Unexpected adverse drug reaction

An unexpected ADR is an ADR which, the nature or severity of which is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the appropriate reference documents*, e.g.* Investigator's Brochure for lenalidomide and summary of product information for allopurinol.

7.1.5. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

7.2. Documentation and follow-up of adverse events

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the CRF. AEs occurring up to 28 days after the last dose of the IMP will be reported. For documentation of AEs of special interest see table in section *7*.

For the procedure of SAE-reporting see section 7.3 and section 6.1.5 for safety analyses.

7.2.1. Documentation of adverse events, infections and adverse drug reactions

All AEs (all CTC grades) will be documented in the CRF including all information listed below. AEs occurring up to 28 days after the last dose of the IMP will be reported. Exempted are AEs of special interest and those AEs explicitly mentioned in Section 7.1.1.

The AE is documented in the CRF including the following information:

- Date and time of onset and resolution
- Severity
- Causal relationship with IMP / study treatment
- Seriousness
- Interruption or withdrawal of study treatment and other measures taken

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, no further improvement can be expected, or the study has been terminated for the trial subject concerned.

Preexisting diseases (before administration of the IMP) are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

Infectious complications have a significant effect on the clinical course of CLL-Patient.

It may be difficult to distinguish between the occurrence of infections related to the disease itself or to the consequences of therapy. As new agents and treatment approaches such as lenalidomide maintenance are tested in clinical settings, it is important to evaluate not only the effect of these regimes on the disease itself, but to assess the influence of these agents on the immune function and resulting infectious complications as well. It is important to identify discrete patient subsets that are at increased risk for infections.

Infections should be reported and categorized as bacterial, viral or fungal. For identification of the underlying pathogen further diagnostic is required and should be documented on the CRF. Standardized recommendations for empirical management and targeted surveillance of infections are listed below.

The severity of infection should be quantified according to the common Toxicity Criteria Version 4.0. (see Appendix 11.14). All grades of infections are documented.

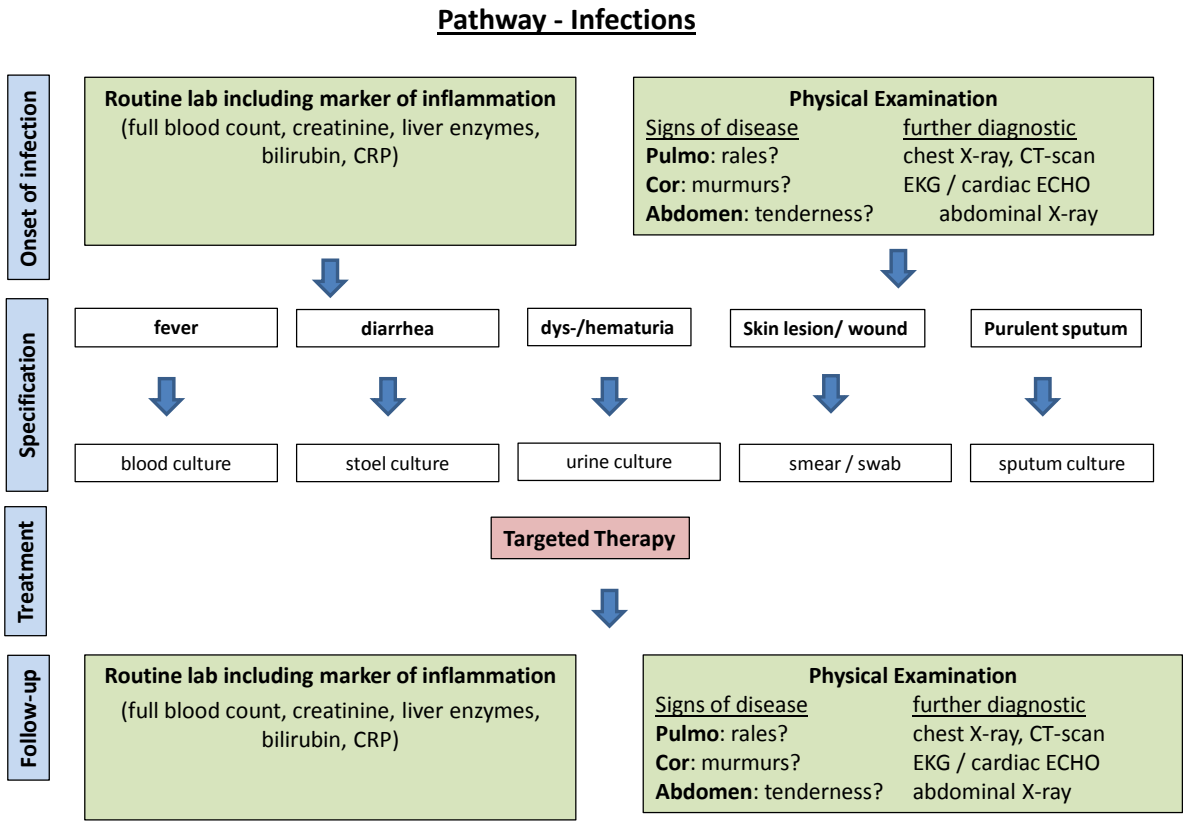

Figure 2: Infection pathway

7.2.2. Severity of the adverse event

The NCI CTC Version 4.0 will be used to describe and classify the AEs. The investigator will classify the severity of AEs as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living (ADL).

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

7.2.3. Causal relationship between AE and IMP

The investigator will assess every AE whether a causal relationship with the IMP can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the IMP, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of

efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed.

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not related:	The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Related:	The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
Not evaluable:	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

An ADR is suspected if the causal relationship is related or not evaluable. Events assessed as ‘unrelated’ are not suspected ADRs.

7.3. Reporting of SAE, pregnancy and changes in risk-benefit assessment

7.3.1. Reports from the investigator to the sponsor

As outlined above the investigator must complete the Serious Adverse Event Report Form and send it by fax within 24 hours investigator becoming aware of the event to the sponsor`s designee:

GCLLSG study office (fax-number: +49-221-478-86886).

All serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration until the study is closed. The definition and reporting requirements of the EU Good Clinical Practice Guideline CPMP/ICH/135/95 will be adhered to.

The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site. Follow-up information should be sent to the sponsor or designee by fax, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resubmitted (with the new information highlighted and a new date provided). The follow-up report should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or discontinued study participation. The form and fax confirmation sheet must be retained.

The investigator will also inform the sponsor without delay about any pregnancy that occurs during the trial, i.e. within 24 hours of being made aware of such. This will be documented on

a separate pregnancy form. The pregnant trial subject will be asked to give separate informed consent for pregnancy follow up.

Assessment of event by sponsor

All cases of suspected SAEs are assessed by the sponsor with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments.

In double-blind trials, the trial subject's treatment must be unblinded if the investigator or sponsor assesses the event as serious and possibly related and if the sponsor assesses the event as unexpected (see Section 7.3.2).

7.3.2. Unblinding when treatment is blinded

For the purpose of regulatory reporting, GCLLSG safety management will determine the expectedness of reported events suspected of being related to lenalidomide based on the Investigator Brochure.

For countries within the European Union, GCLLSG safety management will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, AEs in accordance with the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements. GCLLSG safety management shall notify the Investigator of the following information: Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, i.e., suspected unexpected serious adverse reaction (SUSAR). purposes. If an SAE is assessed as a SUSAR by the GCLLSG safety management, the trial treatment will be unblinded within the IVR-System in the individual trial subject to verify causality before reporting the event to the ethics committee and the competent authorities. This means that the trial subject's treatment is unblinded and the potential SUSARs is reassessed, to decide whether there really is an at least possible causal relationship and whether the event should therefore be classified as a SUSAR. The procedure for causality assessment and unblinding and for the sponsor's assessment will be done according to the GCLLSG SOP for SAE Management and SUSAR Reporting).

7.3.3. Notification of ethics committee and competent supreme federal authority

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor to the competent authorities and the ethics committee. Reference for safety information will be in the current version of the Investigators Brochure.

<u>Fatal and life-threatening SUSARs</u>

The competent authorities and the ethics committee responsible must be informed by the sponsor of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the competent supreme federal authority and the local competent authority and the ethics

committee within a further 8 days. Furthermore, if a trial subject dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

SUSARs that are not fatal or life-threatening

The competent authorities and the ethics committee responsible will be informed without delay by the sponsor of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

SUSAR reporting in the participating countries (Austria, Germany, Italy, Netherlands and Spain) will be done according to the country specific requirements and according to the current local law.

7.3.4. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the sponsor will inform the ethics committee responsible and the competent authorities of all other member states of the EU or EEA where the trial is being conducted, of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. These consist of especially:

- Individual reports of expected serious ADRs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SADRs
- SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”)
- Factors emerging in connection with trial conduct or the development of the IMP that may affect the safety of persons concerned.

7.3.5. Informing the Data Safety Monitoring Board

Following the DSMB charter, the DSMB will be informed of all safety-relevant events by the GCLLSG as the sponsor’s representative. DSMB will receive all fatal SAEs immediately, and every six months all SARs including all SUSARs, all second primary malignancies reported as SAEs and a line listing of all SAEs that occurred in the study.

7.3.6. Informing the investigators

The GCLLSG informs investigators of all SUSARs including all relevant further information within the periods set by the supreme federal authority.

If new information becomes known that is different from the scientific information given to the investigator, all investigators will be informed of this by the GCLLSG.

7.3.7. Informing the marketing authorisation holder

The GCLLSG will also inform the marketing authorization holder about all SAEs and SUSARs including information reported to the competent supreme authority and ethics committee in accordance with contractual agreements. Details of this reporting will be covered in a contract between the Sponsor and Celgene.

7.4. Development Safety Update report of trial subjects

Once per year or on demand, the GCLLSG will supply a report on the safety of trial subjects in accordance with GCP §13 and ICH E2F guideline “Note for guidance on development safety update reports” with all relevant information during the reference period to the competent supreme federal authority, the ethics committee responsible and the competent authorities of all other member states of the EU or EEA where the trial is being conducted. The GCLLSG will supply the report within 60 days of one year after the reference date (data-lock point).

8. Use of trial findings and publication

8.1. Final report

The BfArM: Bundesinstitut für Arzeneimittel und Medizinprodukte, Bonn as well as the appropriate Health Authorities and ethics committees will be informed within 90 days that the trial has officially ended.

Within one year of the completion of the trial, the competent authorities and the ethics committees will be supplied with a summary of the final report on the clinical trial containing the principle results.

8.2. Publication

It is planned to publish the trial results in a scientific journal and present results at German or international conferences. Publication of the results of the trial as a whole is intended. The trial will also be registered in a public register. Any published data will observe data protection legislation covering the trial subject and investigators. Response rates or individual findings at individual trial sites are known only to the sponsor. Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

9. Amendments to the trial protocol

Any modifications to the protocol which may have an impact on the conduct of the study or the potential benefit of the study, or which may affect subject safety – including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects (cf. § 10, Abs. 1 GCP-V for the decision criteria) – will require a formal written amendment to the protocol. Such an amendment will be agreed upon by the sponsor/director of clinical investigation. It requires a new application to the responsible authority and to the responsible ethics committee before implementation, according to §10, Abs. 2 to 4 GCP-V.
Administrative or technical changes of the protocol such as minor corrections and/or clarifications that neither have effect on the way the study is to be conducted, nor on the risk–benefit ratio, will be agreed upon by the sponsor and the investigator(s) and will be documented in a memorandum to the protocol. The ethics committee responsible may be notified of such changes at the discretion of the director of clinical investigation.

The sponsor/director of clinical investigation has to assure, that all amendments have been added to the study documents at any site involved in the trial.

10. References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446-5456.
2. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature;475:101-105.
3. Dores GM, Anderson WF, Curtis RE, et al. Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. Br J Haematol. 2007;139:809-819.
4. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006;107:265-276.
5. Binet JL, Caligaris-Cappio F, Catovsky D, et al. Perspectives on the use of new diagnostic tools in the treatment of chronic lymphocytic leukemia. Blood. 2006;107:859-861.
6. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48:198-206.
7. Rai KR, Wasil T, Iqbal U, et al. Clinical staging and prognostic markers in chronic lymphocytic leukemia. Hematol Oncol Clin North Am. 2004;18:795-805, vii.
8. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910-1916.
9. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood. 1999;94:1840-1847.
10. Hamblin TJ, Davis ZA, Oscier DG. Determination of how many immunoglobulin variable region heavy chain mutations are allowable in unmutated chronic lymphocytic leukaemia - long-term follow up of patients with different percentages of mutations. Br J Haematol. 2008;140:320-323.
11. Hallek M, Wanders L, Ostwald M, et al. Serum beta(2)-microglobulin and serum thymidine kinase are independent predictors of progression-free survival in chronic lymphocytic leukemia and immunocytoma. Leuk Lymphoma. 1996;22:439-447.
12. Hallek M, Langenmayer I, Nerl C, et al. Elevated serum thymidine kinase levels identify a subgroup at high risk of disease progression in early, nonsmoldering chronic lymphocytic leukemia. Blood. 1999;93:1732-1737.
13. Crespo M, Bosch F, Villamor N, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med. 2003;348:1764-1775.
14. Hamblin TJ, Orchard JA, Ibbotson RE, et al. CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood. 2002;99:1023-1029.
15. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood. 2006;107:885-891.
16. Elter T, Gercheva-Kyuchukova L, Pylylpenko H, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. Lancet Oncol.
17. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23:4079-4088.
18. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008;112:975-980.

19. Foon KA, Boyiadzis M, Land SR, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27:498-503.
20. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet;376:1164-1174.
21. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood. 2007;109:405-411.
22. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol;29:3559-3566.
23. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27:4378-4384.
24. Koppler H, Heymanns J, Pandorf A, Weide R. Bendamustine plus mitoxantrone--a new effective treatment for advanced chronic lymphocytic leukaemia: results of a phase I/II study. Leuk Lymphoma. 2004;45:911-913.
25. Lin TS. Novel agents in chronic lymphocytic leukemia: efficacy and tolerability of new therapies. Clin Lymphoma Myeloma. 2008;8 Suppl 4:S137-143.
26. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program;2010:481-488.
27. Fink A, Pflug N, Boettcher S, Winkler D, Buehler A, Ritgen M, Fischer K, Eichhorst B, Wendtner CM, Mendila M, Wenger M, Doehner H, Kneba M, Stilgenbauer S, Hallek M. Prediction of Poor Outcome in CLL Patients Treated with FCR (Fludarabine, Cyclophosphamide, Rituximab) in the CLL8 Trial of the German CLL Study Group (GCLLSG). ASH 2011. 2011.
28. Fink AM, Bottcher S, Ritgen M, et al. Prediction of poor outcome in CLL patients following first-line treatment with fludarabine, cyclophosphamide and rituximab. Leukemia.
29. Wierda WG, O'Brien S, Wang X, et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. J Clin Oncol. 2009;27:1637-1643.
30. Catovsky D, Fooks J, Richards S. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. A report from the MRC CLL 1 trial. MRC Working Party on Leukaemia in Adults. Br J Haematol. 1989;72:141-149.
31. Tsimberidou AM, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer. 2009;115:373-380.
32. Kwok M, Rawstron, A. C., Varghese, A. & Hillmen, P. Minimal residual disease is a predictor for progression-free and overall survival in chronic lymphocytic leukemia (CLL) that is independent of the type or line of therapy [abstract]. Blood 114, a540 (2009).
33. Böttcher S RM, Fischer K, Stilgenbauer S, Busch R, Fingerle-Rowson G, Fink AM, Bühler A, Zenz T, Wenger M, Mendila M, Wendtner CM, Eichhorst B, Döhner H, Hallek M, Kneba M. Minimal residual disease quantification is an independent predictor of progression free and overall survival in chronic lymphocytic leukemia. A multivariate analysis from the randomized GCLLSG CLL8 trial. JCO accepted, in Print.
34. Bottcher S, Stilgenbauer S, Busch R, et al. Standardized MRD flow and ASO IGH RQ-PCR for MRD quantification in CLL patients after rituximab-containing immunochemotherapy: a comparative analysis. Leukemia. 2009;23:2007-2017.
35. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia. 2007;21:956-964.

36. Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol. 2005;23:2971-2979.
37. Rawstron AC, Kennedy B, Evans PA, et al. Quantitation of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy. Blood. 2001;98:29-35.
38. Moreno C, Villamor N, Colomer D, et al. Clinical significance of minimal residual disease, as assessed by different techniques, after stem cell transplantation for chronic lymphocytic leukemia. Blood. 2006;107:4563-4569.
39. Lamanna N, Jurcic JG, Noy A, et al. Sequential therapy with fludarabine, high-dose cyclophosphamide, and rituximab in previously untreated patients with chronic lymphocytic leukemia produces high-quality responses: molecular remissions predict for durable complete responses. J Clin Oncol. 2009;27:491-497.
40. Lamanna N, Weiss MA. Consolidation and maintenance rituximab therapy in chronic lymphocytic leukemia. Curr Oncol Rep. 2008;10:363-364.
41. Schweighofer CD, Hallek M, Wendtner CM. Eradication of minimal residual disease in chronic lymphocytic leukemia. Curr Hematol Malig Rep. 2008;3:54-60.
42. Schweighofer CD, Ritgen M, Eichhorst BF, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). Br J Haematol. 2009;144:95-98.
43. Montillo M, Tedeschi A, Miqueleiz S, et al. Alemtuzumab as consolidation after a response to fludarabine is effective in purging residual disease in patients with chronic lymphocytic leukemia. J Clin Oncol. 2006;24:2337-2342.
44. O'Brien S, Kay NE. Maintenance therapy for B-chronic lymphocytic leukemia. Clin Adv Hematol Oncol;9:22-31.
45. Del Poeta G, Del Principe MI, Buccisano F, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. Cancer. 2008;112:119-128.
46. Hainsworth JD, Vazquez ER, Spigel DR, et al. Combination therapy with fludarabine and rituximab followed by alemtuzumab in the first-line treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer. 2008;112:1288-1295.
47. Ramsay AG, Johnson AJ, Lee AM, et al. Chronic lymphocytic leukemia T cells show impaired immunological synapse formation that can be reversed with an immunomodulating drug. J Clin Invest. 2008;118:2427-2437.
48. Wu L, Adams M, Carter T, et al. lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res. 2008;14:4650-4657.
49. Wu L, Parton A, Lu L, Adams M, Schafer P, Bartlett JB. Lenalidomide enhances antibody-dependent cellular cytotoxicity of solid tumor cells in vitro: influence of host immune and tumor markers. Cancer Immunol Immunother;60:61-73.
50. Chang DH, Liu N, Klimek V, et al. Enhancement of ligand-dependent activation of human natural killer T cells by lenalidomide: therapeutic implications. Blood. 2006;108:618-621.
51. Wendtner CM, Hillmen P, Mahadevan D, et al. Final results of a multicenter phase 1 study of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia. Leuk Lymphoma.
52. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006;24:5343-5349.
53. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008;111:5291-5297.

54. Shanafelt T TH, Hanson C, Zent C, Leis J, Call T, LaPlant B, Bowen D, Laumann K, Jelinek D, Kay N. Lendalidomide Consolidation After First-Line Chemoimmunotherapy for Patients with Previously Untreated CLL ASH abstract 1379. 2010.
55. Wendtner CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission--experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia. 2004;18:1093-1101.
56. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood. 2003;101:6-14.
57. Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol. 2000;35:181-200.
58. Yancik R, Ganz PA, Varricchio CG, Conley B. Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. J Clin Oncol. 2001;19:1147-1151.
59. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16:622-626.
60. Waldman E, Potter JF. A prospective evaluation of the cumulative illness rating scale. Aging (Milano). 1992;4:171-178.
61. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc. 1995;43:130-137.
62. Firat S, Byhardt RW, Gore E. Comorbidity and Karnofksy performance score are independent prognostic factors in stage III non-small-cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 2002;54:357-364.
63. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol. 1998;16:1582-1587.
64. Chen H, Cantor A, Meyer J, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer. 2003;97:1107-1114.
65. Galustian C, Dalgleish A. Lenalidomide: a novel anticancer drug with multiple modalities. Expert Opin Pharmacother. 2009;10:125-133.
66. Tohnya TM, Ng SS, Dahut WL, et al. A phase I study of oral CC-5013 (lenalidomide, Revlimid), a thalidomide derivative, in patients with refractory metastatic cancer. Clin Prostate Cancer. 2004;2:241-243.

11. Appendices

11.1. Trial sites and principle investigators

See separate pdf document

11.2. PFS Independent Review Committee

See separate pdf. document

11.3. Protocol Agreement Form

See separate pdf document

11.4. Data Safety Monitoring Board

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Prof. Dr. Emili Montserrat, Institute of Hematology and Oncology at the Hospital Clinic of Barcelona, University of Barcelona, EMONTSE@clinic.ub.es

11.5. Study laboratories and other technical resources

Central molecular genetic reference testing (fluorescence in situ hybridization (FISH) and analysis of the IGHV status:

Shipping address: Mo - Thurs

Prof. Dr. S. Stilgenbauer

Laboratory Molecular Genetics

Department of Internal Medicine III

University Hospital Ulm

Albert Einstein-Allee 23

D-89081 Ulm

Tel.: +49 (0)731/500-45813

Fax: +49 (0)731/500-45825

MRD testing by quantitative highly sensitive flow cytometry (MRD flow) for the presence of minimal residual disease (MRD) and T/NK-cell analyses.

Shipping address: **Mo - Thurs**

Dr. S. Böttcher/ Dr. M. Ritgen / Prof. M. Kneba

PD Dr. S. Böttcher, Dr. M. Ritgen, Prof. Dr. Dr. M. Kneba

Durchflußzytometrisches Labor

Hämatologielabor Kiel, Sektion für Hämatologische Spezialdiagnostik

der Medizinischen Klinik II

Universitätsklinikum Schleswig-Holstein, Campus Kiel

Langer Segen 8-10

24105 Kiel

Tel.: +49 (0) 431-500-24966

Fax: +49 (0) 431-500-24964

Bone marrow biopsy will be forwarded to Prof Klapper:

Prof. Dr. Wolfram Klapper

Institut für Pathologie

Christian-Albrechts-Universität zu Kiel

Arnold-Heller-Straße 3, Haus 14

24105 Kiel

Telefon: +49 (0)431 597 3399

Fax: +49 (0)431 597 3426

Email: wklapper@path.uni-kiel.de

Shipping address: **Mo - Thurs**

Dr. M. Ritgen, Prof. Dr. Dr. M. Kneba

Durchflußzytometrisches Labor

Hämatologielabor Kiel, Sektion für Hämatologische Spezialdiagnostik

der Medizinischen Klinik II

Universitätsklinikum Schleswig-Holstein, Campus Kiel

Langer Segen 8-10

24105 Kiel

Tel.: +49 (0) 431-500-24966

Fax: +49 (0) 431-500-24964

Immunophenotyping, CD38/ZAP-70 Expression and caryotyping

Shipping address: **Mo - Thurs**

Hematology and Oncology
Prof.. Dr. K.-A. Kreuzer

Dpt. I of Internal Medicine

Building 13 (LFI), Level 4, Room 410

University at Cologne

Kerpener Strasse 62

50924 Köln

Tel.: ++49 (0)221 478-97382 or Tel.: +49 (0)221 478-3795

Fax: ++49 (0)221 478-97383

Serum parameters (thymidine kinase, β_2 microglobulin)(will be forwarded to

Shipping address: **Mo - Thurs**

Institute of Clinical Chemistry

Dr. med. Gebhart Malchau

Universitätsklinikum Köln

Tel: +49-221-478-5290

Fax: +49-221-478-5273

11.6. Sample labels for investigational medicinal product (IMP)

See separate pdf document

11.7. Pre-Study Informed Consent Form for Biomarker and Cytogenetic Testing

See separate pdf document

11.8. Subject information sheet and informed consent form

See separate pdf document

11.9. Confirmation of insurance

All trial subjects enrolled are insured in accordance with § 40 AMG under the group insurance contract of Cologne University Hospital with

HDI Gerling Industrie Versicherung AG

Postfach 101027

40001 Düsseldorf

Germany

Insurance NO: 57 01030903010

The headquarters, policy number and telephone and fax number will be included in the subject information sheet.

11.10. Conditions of insurance

See separate pdf document

11.11. CIRS Evaluation Form

See separate pdf document

11.12. Binet/Rai staging system

See separate pdf document

11.13. ECOG performance status scale

Score	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 our work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

11.14. Adverse effects (NCI-CTC criteria v4.0)

See separate pdf document

11.15. World Medical Association Declaration of Helsinki

See separate pdf document

11.16. Approval by the responsible ethics-committee

See separate pdf document

11.17. Investigator's brochure or summary of product characteristics

See separate pdf document

11.18. Lenalidomide Education and Counseling Guidance Document

See separate pdf document

11.19. Lenalidomide Information Sheet

See separate pdf document

11.20. Lenalidomide Pregnancy Prevention Risk Management Plans

See separate pdf document

11.21. Tumor Lysis Syndrome (Coiffier B et al.)

See separate pdf document

11.22. Guidelines for the diagnosis and treatment of chronic lymphocatic leukemia

A report from the International Workshop on CLL updating the Natinal Cancer Working group guidelines of 1996

See separate pdf document