II. Synopsis

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Title of the clinical trial	CLL-Frail – A prospective, multicenter phase II trial of acalabrutinib in very old (≥80y) or frail CLL-Patients
Participating countries	Germany, Austria
Indication	Very old (≥80y) or frail patients with treatment-naïve or relapsed/refractory chronic lymphocytic leukemia (CLL)
Phase	Phase II clinical trial
Trial design, methodology	Prospective, multicentre, phase II trial
Number of patients	Approximately 50 eligible patients
Trial objectives	The primary objective of this trial aims to show the efficacy of acalabrutinib in a cohort of CLL-patients ≥80 years or with a FRAIL scale score >2 via the patient's own assessment.

The secondary objective of this trial is to show the safety of acalabrutinib as well as feasibility of conducting a trial in this so far underrepresented patient group.

Rationale

The treatment landscape for CLL underwent profound changes in recent years with the introduction of novel agents. The orally available Bruton's tyrosine kinase (BTK) inhibitor ibrutinib was proven to be a highly efficacious treatment with acceptable, moderate toxicities and has subsequently revolutionized CLL treatment. The Resonate-2 trial investigated ibrutinib vs chlorambucil monotherapy in 269 previously untreated patients and reported significantly improved progression free survival (PFS) 70% vs 12% and an improved overall survival (OS) of 83% vs 68% at 5 years[1].

The ILLUMINATE trial investigated the use of ibrutinib in combination therapy with obinutuzumab versus chlorambucil plus obinutuzumab and reported similar results with a median PFS of not reached vs 19 months after a median follow up of 31.3 months[2]. Whereas the Alliance trial compared the three treatment regimen bendamustine plus rituximab vs. ibrutinib monotherapy vs ibrutinib plus rituximab and was also able to show a significantly improved PFS rate (74% vs 87% vs 88%) of ibrutinib versus chemoimmunotherapy after 2 years of therapy in older patients >65 year[3].

However, available data for very old or frail patients are still sparse. The aforementioned trials all reported median ages of 73 (70% of patients being older than 70 years), 71 (IQR 66-76) and 71 years respectively[2–4]. Furthermore, recently published retrospective real-world-analyses showed a rate of 52,1% of elderly patients interrupting or discontinuing treatment within the first year of treatment with ibrutinib. 32,4% of elderly patients discontinued treatment due to adverse events[5].

Even though patients ≥80 years are the fastest growing age group in Western populations and represent around 20% of the general CLL-population they are only represented at 5% in clinical trials[6]. The main reasons for this are rigid exclusion criteria with a specified fitness/ECOG level, a limited severity of allowed comorbidities, which most of older patients at this age suffer from, and/or a general hesitancy of older patients to participate in clinical trials with frequent visits. Furthermore, elderly and frail patients tend to visit outpatient local clinics rather than large centralized facilities like university hospitals. As there is a lack of data on how to recruit and treat these patients in clinical trials, further evaluation of this increasing patient population is urgently needed.

Acalabrutinib has recently been introduced as a novel, more selective BTK inhibitor. A phase-I/II-trial in 134 patients with relapsed/refractory CLL showed an overall response rate of 93% and most notably of 85% in 23/27 high-risk CLL-patients with del17p[7]. A recent analyses of the phase-III ELEVATE-TN trial investigated acalabrutinib + obinutuzumab vs. acalabrutinib monotherapy vs. chlorambucil + obinutuzumab in treatment-naïve CLL reported a median progression free survival of not reached in acalabrutinib-containing regimen vs. 22.6 months after a median follow-up of 28 months. The safety profile showed a well tolerable regimen[8].

This trial therefore aims to evaluate an efficacious and more tolerable therapy regimen with acalabrutinib in this so far underrepresented age group.

However numerical age only does not strictly correlate with a patient's physical fitness and common fitness scores such as the ECOG Performance Status as these do not include a geriatric assessment to account for different aspects of the heterogenic aging process[9]. Additionally, a frailty phenotype comprised of unintentional weight loss (10 lbs. in past year), self-reported exhaustion, weakness (grip strength), slow walking

speed, and low physical activity has been found to be associated with a significant impact on overall survival[10]. Study participants will therefore be assessed and included into the study alluding to Fried's frailty phenotype[11] during screening and at different time points throughout the study to further study the impact of frailty in the elderly. Since the ability to assess the frailty phenotype is largely dependent on resources and adequate training, this trial will use the closely related and validated FRAIL scale to assess frailty in this cohort[12,13].

After the follow-up period, patients will be encouraged to be included in the GCLLSG's registry to collect further long-term follow-up data.

Study end points

Primary endpoints:

- Overall response rate (ORR) at initial response assessment (cycle 7, day 1 = approx. 6 months after initiation of therapy).

Secondary end points:

- ORR at final restaging (cycle 25, day 1 = approx. 24 months after initiation of therapy).
- Overall survival (OS).
- Progression free survival (PFS).
- Event-free survival (EFS).
- Duration of response.
- Time to next CLL treatment (TTNT).
- Feasibility parameters:
    - Modification of treatment and reasons.
    - Treatment discontinuation: early discontinuation of treatment and reasons.
    - Treatment exposure: total cumulative dose, dose intensity, time on treatment (any dose), time on treatment (full dose), days with 0 dose.

- Safety parameters: Type, frequency, and severity of
  - adverse events (AEs) and
  - adverse events of special interest (AESI) including falls and delirium as typical adverse geriatric outcomes and their relationship to study treatment.

Exploratory endpoints

- Health-related quality of life (by EORTC QLQC30 and QLQ-CLL17 questionnaires).
- Exploratory evaluations of potential associations between various baseline markers and clinical outcome parameters.
- Frailty-assessment via FRAIL scale score at initial response assessment and final restaging.

Criteria for evaluation

Efficacy

- Lymph nodes, spleen and liver measurements by physical examination.
- Ultrasound at initial response assessment at initial response assessment (IR) at cycle 7 day 1 (= approx. 6 months) and at final restaging (RE) at cycle 25 day 1 (= approx. month 24 after initiation of therapy) and additionally if clinically indicated.
- Computed tomography (CT) or Magnetic Resonance Imaging (MRI) scans for response assessment are preferred but remain optional.
- Complete blood count (CBC).
- Assessment of constitutional symptoms.
- Survival status.
- Survey of start and type of next treatment for CLL.

Safety

- Clinical laboratory evaluations.
- Concomitant medications.
- AEs by NCI CTCAE Version 5.

Baseline marker

- Physical examination.
- Peripheral blood count/serum chemistry.
- Central and local results of immunophenotyping (for confirmation of CLL diagnosis), serum parameters (beta-2-microglobulin and thymidine kinase), cytogenetics (FISH), TP53 and IGHV mutational status and genome sequencing.
- Ultrasound scan of peripheral and abdominal lymphadenopathy, liver and spleen using sonography (head/neck, chest, abdomen and pelvis/inguinal region).
- ECOG Performance Status.
- Assessment of FRAIL scale score (see below).
- Cumulative Illness Rating Scale (CIRS).
- Assessment of constitutional symptoms.
- Concomitant medication.
- Medical history, emphasize on cardiac/vascular/metabolic morbidity and atypical/opportunistic infections three years prior to baseline.
- ECG.
- Health-related quality of life by EORTC QLQC30 and QLQ-CLL17 questionnaires.

- Bone marrow aspirate/biopsy (if clinically indicated to prove association with CLL infiltration).
- Height/Weight/Body surface area (BSA)
- HIV/HBV/HCV test.

Frailty

Patients will be asked to fill out a 5-item questionnaire.

- **F**atigue: How often have you felt fatigued/tired over the last four weeks?
  - All of the time/ Most of the time (1 point)
  - Some of the time / A little of the time / None of the time (0 points)
- **R**esistance: Do you have any difficulties walking up 10 steps alone without rest and aids?
  - Yes (1 point)
  - No (0 points)
- **A**mbulation: Do you have any difficulties walking several hundred meters alone without rest and aids?
  - Yes (1 point)
  - No (0 points)
- **I**llnesses: Do you have more than 5 out of these 11 illnesses?
  - hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, history of heart attack/myocardial infarction, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease (Yes: 1 point / No: 0 points)

- **L**oss of weight: Have you lost more than 5% of your weight in the past 12 months?
  - Yes (1 point)
  - No (0 points)

Frailty will be assessed at baseline, initial response assessment and final restaging during the study and evaluated based on the FRAIL Scale:

3 or greater = frailty; 1 or 2 = prefrail.

Target Population

To account for an increasing number of fit CLL patients ≥80 years where numerical age does not equal biological age, the study population will consist of at least 50% patients with a FRAIL scale score >2. With an expected study population of approximately 50 patients after screening, this will lead to a maximum of approximately 25 patients with a FRAIL scale score <3 to be analysed within the CLL-Frail-trial.

Patients must meet the following criteria:

Inclusion Criteria

1. Age ≥80 years AND/OR considered too frail for intensive/standard treatment defined by a frailty score of >2 on the FRAIL scale via the patient´s assessment.
2. Have documented CLL requiring treatment according to iwCLL 2018 criteria[14].
3. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements.
4. GFR >30ml/min directly measured with 24hr urine collection, calculated according to the modified formula of Cockcroft and Gault

(for men: GFR ≈ ((140 – age) x bodyweight)/ (72 x creatinine), for women x 0, 85) or an equally accurate method.

i. **Please note:** Patients currently on hemodialysis are excluded from participating in the trial.

5. Adequate liver function as indicated by a total bilirubin ≤ 3 x, AST/ ALT ≤ 3 x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome.
6. Adequate marrow function independent of growth factor or transfusion support as follows, unless cytopenia is due to marrow involvement of CLL:
   i. Absolute neutrophil count ≥ 1.0 × 10^9/L.
   ii. Platelet counts ≥ 30 × 10^9/L; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator); platelet count should be ≥ 10 × 10^9/L if there is bone marrow involvement.
   iii. Total haemoglobin ≥ 9 g/dL (without transfusion support, unless anaemia is due to marrow involvement of CLL).
7. Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every month until 12 months after last month of treatment), negative testing for hepatitis C RNA within 6 weeks prior to registration.
8. Life expectancy ≥ 3 months.
9. Maximum of 1 previous treatment for CLL.

10. In case of a recent previous treatment, patients must have recovered from acute toxicities and treatment regimen must be stopped within the following time periods before start of the study treatment in the CLL-Frail trial:
    i. chemotherapy ≥ 28 days
    ii. antibody treatment ≥ 14 days
    iii. kinase inhibitors (see also exclusion criterion 6), BCL2-antagonists or immuno-modulatory agents ≥ 3 days
    iv. corticosteroids may be applied until the start of the study therapy, these have to be reduced to an equivalent of ≤ 20mg prednisolone per day during treatment.
11. Signed informed consent and, in the investigator's judgment, able to comply with the study protocol.

Exclusion criteria

1. >1 prior CLL-specific therapy (except corticosteroid treatment administered due to necessary immediate intervention; within the last 14 days before start of study treatment, only dose equivalents up to 20 mg prednisolone are permitted).
2. Transformation of CLL to aggressive NHL (Richter's transformation or pro-lymphocytic leukaemia).
3. Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML).
4. Patients with uncontrolled autoimmune haemolytic anaemia or immune thrombocytopenia.
5. Prior exposure to acalabrutinib.

6. Progression during previous treatment with another BTK inhibitor, and/or presence of known mutations associated with resistance to therapy, e.g. Bruton´s Tyrosine Kinase (BTK) and Phospholipase C Gamma 2 (PLCg2).
7. Uncontrolled concomitant malignancy, i.e. any concomitant malignancy that may compromise the assessment of CLL stage and the response assessment of the study treatment.
8. Eastern Cooperative Oncology Group Performance Status (ECOG) performance status >3.
9. Uncontrolled or active infection (including positive SARS-Cov-2 PCR result).
10. Patients with known infection with human immunodeficiency virus (HIV).
11. Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 3 months of screening, or any class 4 cardiac disease as defined by the New York Heart Association Functional Classification at Screening**.**
    i. **Please note:** Subjects with controlled, asymptomatic atrial fibrillation are allowed to enroll on study.
12. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
13. Significantly increased risk of bleeding according to the investigator´s evaluation, e.g. due known bleeding diathesis (e.g. von-Willebrandt´s disease or hemophilia), major surgical procedure ≤ 4 weeks or stroke/intracranial hemorrhage ≤ 6 months.

14. Use of investigational agents which might interfere with the study drug within 28 days prior to registration for study screening.
15. Requirement of therapy with strong CYP3A4 inhibitors/inducers or anticoagulant with phenprocoumon (marcumar) or other vitamin K-antagonists.
    i. **Please note:** Switch to alternative anticoagulants for vitamin K antagonists is permitted.
16. Inability to swallow tablets.
17. Legal incapacity.
18. Prisoners or subjects who are institutionalized by regulatory or court order.
19. Persons who are in dependence to the sponsor or an investigator.

Name of investigational medicinal products (IMPs)	**Acalabrutinib** (ACP-196, trade name: Calquence®) One 100mg capsule to be taken twice daily (BID) every 12 hours.
Reference safety information	Summary of product characteristics (SmPC)

Treatment schedule

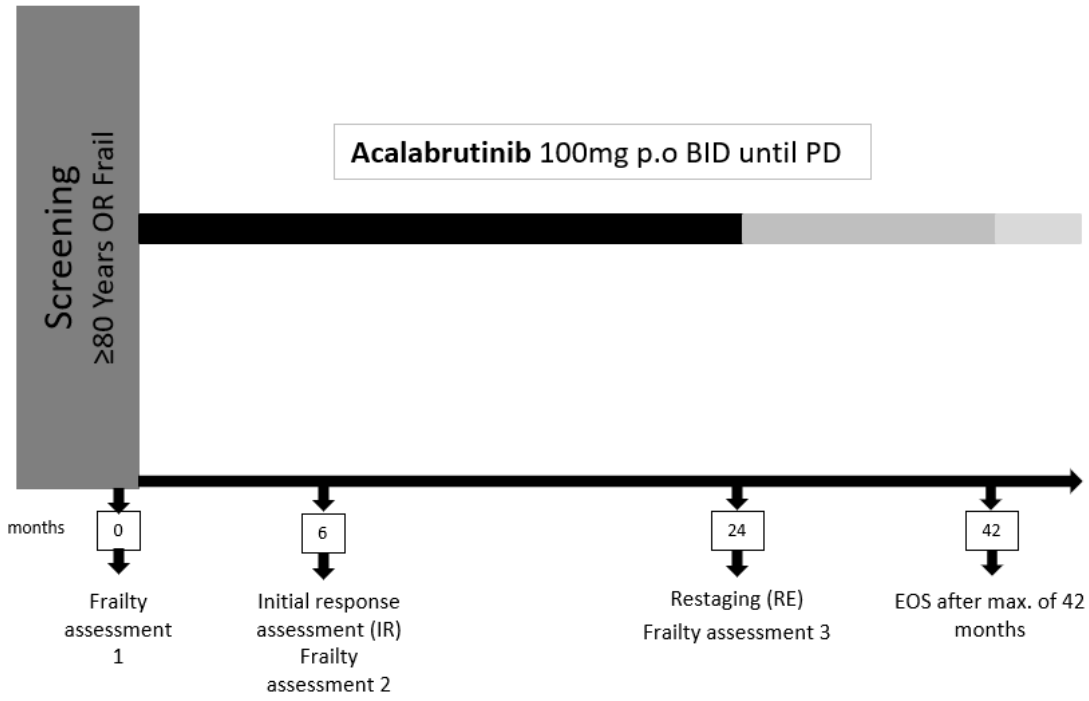

Figure 1: Treatment schedule

Investigational medicinal product – dosage and method of administration	**Acalabrutinib (ACP-196) monotherapy (I)** Acalabrutinib will be administered as a daily oral dosage of 100mg twice daily starting on cycle 1 day 1 until disease progression or intolerance. One cycle of treatment will consist of 28 days. Cycle 1 – PD Days 1-28 acalabrutinib 100 mg p.o. BID

Duration of treatment

Acalabrutinib will be administered for six cycles during which frequent monitoring of patients will take place.

Patients who respond to therapy and do not show signs of intolerable toxicity will continue with treatment for up to 24 cycles (= approx. 24 months total) with staging visits every 3 cycles (= approx. three months) until PD or intolerable toxicity. Treatment may be continued beyond those 24 months in patients who respond to therapy and tolerate treatment with acalabrutinib according to the discretion of the treating physician.

Patients will be followed up every three months until death or end of study (EOS), whichever occurs first.

The end of the clinical trial is defined as the time point once the last patient completed 24 cycles (= approx. 24 months) of therapy or has a progressive disease (PD), whichever occurs first.

Supportive measures for increasing patient accrual and satisfaction

Additionally, the focus will be on the feasibility of performing a clinical trial in this specific patient cohort. Sites may acquire general practitioner monthly laboratory results if these are preferred by the patients. In case of abnormalities as defined in the protocol (including bleeding complications, cardiac arrhythmias, transaminitis) patients will then be referred to their study site for further evaluation.

Additionally, to allow for patient's accrual through hematological clinics in sparsely populated areas and to assure a close monitoring of patients with limited mobility due to frailty, travel costs will be covered by the trial.

Interim safety analysis

To account for age and frailty of this specific patient cohort an interim safety analysis will be performed in the CLL-Frail trial. The interim safety analysis will be triggered once 30 patients have had the opportunity to reach cycle 7, day 1 (approx. 6 months after initiation of therapy). The interim safety analysis will evaluate AEs/AEPIs including but not limited to falls, fractures, cognitive impairment/dementia.

Safety Monitoring/Stopping Criteria

The results from the interim safety analysis and all available data (also from other clinical trials) regarding the drugs used in this trial will be reviewed by the GPI together with the head of the GCLLSG, one statistician and other members of the protocol committee. This review will determine if the recruitment can continue without restrictions on the recruitment rate, if additional safety precautions and monitoring are needed or the trial will be prematurely stopped.

Stopping rules

Any decision to prematurely terminate the study as a whole will be made by the sponsor in accordance with the regulatory and ethical principles. During the study, continual monitoring of efficacy and toxicity will be performed.

Criteria for termination of the study as a whole are:

- An unacceptable profile or incidence rate of adverse events, adverse events of special interest revealed in this or any other study in which the investigational product of this trial is administered.
- Demonstration that the study treatment is ineffective or only insufficiently active.
- Significant number of cases of death associated with the study treatment.

Any other factor that in the view of the sponsor constitutes an adequate reason for terminating the study as a whole.

Statistical methods and analyses

For the analyses, the following patient populations will be defined:

- **Full analysis set (FAS)**: The FAS comprises of all enrolled patients who received at least three complete cycles of trial treatment (efficacy population). This criterion means that at least one dose of acalabrutinib has to be documented for the fourth cycle of

treatment. The FAS shall be used for analysis of all study endpoints except safety and feasibility.

- **Safety population**: The safety population is defined as all subjects enrolled into the study receiving at least one dose of trial treatment, whether withdrawn prematurely or not. The safety population shall be used for evaluating the safety and feasibility endpoints.

The primary efficacy variable (primary endpoint) is the overall response rate (ORR) at cycle 7, day 1 (initial response assessment) which is defined as the proportion of patients achieving a CR, CRi or PR (including PR-L) as response (according to the iwCLL 2018 guidelines). Patients without any documented response assessment will be kept and labelled as 'non-responder' in the analysis.

Sample size calculation

The primary endpoint ORR at initial response assessment, at cycle 7 day 1 (= approx. 6 months) after the introduction of acalabrutinib was used to determine the sample size of the study. The following study assumptions are considered for patients with at least 3 complete cycles of treatment:

- The ORR for a conventional regimen is assumed to be 65% (=P0) with corresponding null hypothesis H0: ORR ≤ 0.65 and alternative hypothesis H1: ORR > 0.65.

- The investigated regimen is considered potentially useful and worthy of further research if the null hypothesis in favor of the alternative hypothesis can be rejected.

- The type I error is set to α = 2.5% and defines the chance that the investigated regimen will be investigated further although the true ORR is lower or equal to 65%.

- The type II error is the chance that an effective treatment will not be studied further. It is assumed to improve the ORR to at least 85% (=P1) with the investigated regimen. The type II error should not exceed β = 10%, so that it is aimed to achieve a power of at least (1 - β) = 90% at the assumed ORR P1.

According to the above determined study parameters a one-sided one-sample binomial-test with an overall significance level of 2.5% provides the sample size N=49, such that statistical significance is achieved with a power of 90%. A screening failure rate of about 10% will be assumed, thus, a total of 55 patients should be screened for the trial.

Sample size calculations were performed with EAST 6 software.

Recruitment strategy

Recruitment is estimated according to the recruitment of prior studies at the GCLLSG. Since about 20% of CLL patients are above 80 years old but only about 5% took part in recent phase II/III-trials at the GCLLSG, an accrual of about 25 patients per year above the age of 80 is estimated. A similar number of patients with frailty is expected to be recruited annually. The international CLL11 trial included roughly 100 patients >80 years over the course of 2 years.

To account for an increasing number of fit CLL patients ≥80 years where numerical age does not equal biological age, the study population will consist of at least 50% patients with a FRAIL scale score >2. This will lead to a maximum of approximately 25 patients with a FRAIL scale score <3 to be analyzed within the CLL-Frail-trial. The study will close recruitment for patients with a FRAIL scale score <3 after an accrual of 25 patients hereof to minimize the risk of a possible over-representation of fit elderly patients ≥80 years.

Study duration

Start of recruitment: Q1/2021

	Expected end of recruitment: Q3/2022 End of study: Q3/2024
GCP conformance	The CLL-Frail trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.