**PROTOCOL Ver 1.5**

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| **TITLE:** | Acalabrutinib in CLL and MCL patients subjected to allogeneic hematopoietic stem cell transplantation (alloSCT) |
| **PROTOCOL NUMBER:** | PLRG12 |
| **STUDY DRUG:** | Acalabrutinib (ACP-196) |
| **EUDRAC NUMBER:** | 2018-003465-33 |
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| **SPONSOR:** | **PLRG – Polish Lymphoma Research Group** |

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## ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AESI | adverse events of special interest |
| AIHA | autoimmune hemolytic anemia |
| alloSCT | allogeneic stem cell transplantation |
| ASCO | American Society of Clinical Oncology |
| ASCT | autologous stem cell transplantation |
| Akt | protein kinase b |
| ALC | absolute lymphocyte count |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| anti-HBc | hepatitis B core antibody |
| anti-HBs | hepatitis B surface antibody |
| aPTT | Activated Partial Thromboplastin Time |
| AST | aspartate aminotransferase |
| ATG | antithymocyte globulin |
| ATP | adenosine triphosphate |
| Bcl-2 | B cell lymphoma 2 |
| BCR | B-cell receptor |
| BCRi | B-cell receptor inhibitors |
| BFR | bendamustine, fludarabine, rituximab |
| BID | twice per day (dosing) |
| BM | bone marrow |
| BP | blood pressure |
| BTK | Bruton tyrosine kinase |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CD | cluster of differentiation (cell surface marker) |

| | |
|---|---|
| CFR | Code of Federal Regulations |
| CI | calcineurin inhibitor |
| CI | cumulative incidence |
| CIs | confidence intervals |
| CLL | chronic lymphocytic leukemia |
| CR | complete response (remission) |
| CrCl | creatinine clearance |
| CRF | case report form |
| CSA | cyclosporine |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome p450 |
| DCR | disease control rate |
| DLI | donor lymphocyte infusion |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| EBMT | European Group for Blood and Marrow Transplantation |
| EBV | Ebstein-Barr virus |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FCM | flow cytometry |
| EFS | event-free survival |
| EMA | European Medicine Agency |
| EMCLN | European MCL Network |
| ESMO | European Society of Medical Oncology |
| FCR | fludarabine, cyclophosphamide, rituximab |
| FDA | Food and Drug Administration |
| FISH | fluorescence in situ hybridization |

| | |
|---|---|
| F | fludarabine |
| FCM | flow cytometry |
| GvHD | graft versus host disease |
| GRFS | GvHD-free and relapse-free survival |
| HBV | hepatitis B virus |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigens |
| HSCT | hematopoietic stem cel transplantation |
| HTC-CI | Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) |
| ICF | informed consent form |
| IEC | independent ethics committee |
| INR | international normalized ratio |
| IgVH | immunoglobulin heavy chain gene variable region |
| Ig | Immunoglobulin |
| IRB | institutional review board |
| irRECIST | immune-related response criteria |
| Itk | interleukin-2 inducible T-cell kinase |
| IWCLL | International Workshop on Chronic Lymphocytic Leukemia |
| IV | intravenous or intravenously |
| IVIG | intravenous immunoglobulin |
| ITP | idiopathic thrombocytopenic purpura |
| LDH | lactate dehydrogenase |
| MCL | Mantle Cell Lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | Minimal Residual Disease |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |

| | |
|---|---|
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NHL | Non Hodgkin lymphoma |
| NK | natural killer (cells) |
| NKT | natural killer T cell |
| NPT | non-protocol anti-tumor therapy |
| NRM | non-relapse mortality |
| MTX | methotrexate |
| HYHA | New York Heart Association Functional Classification |
| ORR | overall response rate |
| OS | overall survival |
| PB | peripheral blood |
| PBMC | peripheral blood mononuclear cells |
| PBSC | peripheral blood stem cells |
| PCR | polymerase chain reaction |
| PFS | progression-free survival |
| PI3K | phosphoinositide 3-kinase |
| PD | pharmacodynamic, pharmacodynamics, or progressive disease |
| P-gp | p-glycoprotein 1 (transporter) |
| PI3K | phosphatidylinositol-3 kinase |
| PK | pharmacokinetic or pharmacokinetics |
| PLRG | Polish Lymphoma Research Group |
| PR | partial response (remission) |
| RIC | reduced-intensity conditioning |
| RR | response rate |
| RNA | ribonucleic acid |
| QD | once per day (dosing) |
| $QT_c$ | corrected QT interval |
| R | rituximab |

| | |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RI | relapse incidence |
| RIC | reduced intensity conditioning |
| R/R | relapsed/refractory |
| SAE | serious adverse event |
| SD | stable disease or standard deviation |
| sIg | surface immunoglobulin |
| SUSAR | suspected unexpected serious adverse reaction |
| Syk | spleen tyrosine kinase |
| TAAE | treatment associated adverse events |
| TEAE | treatment emergent adverse events |
| Th | T helper cell |
| TBI | total body irradiation |
| $T_{reg}$ | regulatory T cells |
| Txk | T cell X chromosome kinase |
| TT | treatment termination |
| ULN | upper limit of normal |
| WHODRUG | World Health Organization Drug Dictionary |
| WOCBP | Women of childbearing potential |

## STUDY SYNOPSIS

| | |
|---|---|
| **Study Title:** | Acalabrutinib in CLL and MCL patients subjected to allogeneic hematopoietic stem cell transplantation (alloSCT) |
| **Protocol Number:** | PLRG12 |
| **Study Drug:** | ACALABRUTINIB (ACP-196) |
| **Phase:** | Phase II |
| **Comparator:** | N/A |
| **Study Centers:** | Subjects will be enrolled in 6 PLRG centers in Poland |
| **Study Objectives:** | **Primary Objective(s):**<br>• Safety:<br>- adverse event (AE) incidence<br>- serious adverse event (SAE) incidence<br>• Response to therapy:<br>- partial and complete remission rate (PR and CR),<br>- minimum residual disease CR (MRD CR) rate assessed by flow cytometry in peripheral blood (PB) and bone marrow (BM)<br>**Secondary Objective(s):**<br>• relapse incidence (RI),<br>• non-relapse mortality (NRM),<br>• progression free survival (PFS),<br>• overall survival (OS), |

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| | **Exploratory Objective(s):**<br>• acute and chronic graft versus host disease (GvHD) incidence,<br>• GvHD-free and relapse-free survival (GRFS),<br>• cytometric assessment of immune cell populations: T cell subsets (CD4+ T cells, CD8+ T cells, Th1, Th2, Th17, T regulatory cells), NK cells, NKT cells and normal B cells, B-regulatory cells |
| **Study Design:** | In this trial II phase multicenter trial we plan to use acalabrutinib before and after allogeneic hematopoietic stem cell transplantation (alloSCT) with reduced intensity conditioning (RIC) in patients with refractory/relapsed MCL and CLL with poor prognostic factors. Acalabrutinib will be used before alloSCT with the intention to reduce tumor burden and after transplant to augment disease control. Since chronic GvHD is mediated by activated B lymphocytes, we also speculate that the drug as a BTK inhibitor may reduce the severity and incidence of chronic graft-versus-host disease (GvHD) after alloSCT, as it was shown for ibrutinib.<br>Best response to therapy and safety issues will be the primary target of this small trial (25 transplanted pts).<br><br>We hypothesize that this treatment will improve the efficacy of the alloSCT – this issue will be addressed by serial minimal residual disease (MRD) evaluation in peripheral blood and bone marrow. This treatment strategy could significantly improve the outcome of poor prognosis MCL and CLL patients. |

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| **Efficacy and Safety Parameters:** | Efficacy parameters:<br>- partial and complete remission rate (PR and CR),<br>- minimum residual disease CR (MRD CR) rate assessed by flow cytometry in peripheral blood (PB) and bone marrow (BM)<br>- relapse incidence (RI),<br>- non-relapse mortality (NRM),<br>- progression free survival (PFS),<br>- duration of response (DOR)<br>- overall survival (OS),<br>- GvHD-free and relapse-free survival (GRFS),<br><br>Safety parameters:<br>- adverse event (AE) incidence<br>- serious adverse event (SAE) incidence |
| **Pharmacodynamic, Pharmacokinetic and Biomarker Parameters:** | N/A |
| **Sample Size:** | 40 patients will be enrolled, and approximately 25 patients will respond to therapy and undergo allogeneic Stem Cell Transplant. |
| **Inclusion Criteria:** | 1. Men and women ≥ 18 years of age.<br>2. Relapsing / refractory BTK-inhibitors naïve CLL patients meeting IWCCL criteria for requiring treatment:<br>a. after 1-4 therapy lines if del 17 or p53 mutation in >10% of analyzed CLL cells (PB or BM) or<br>b. after 2-4 therapy lines if high risk CLL (refractory or less than 24 months response to the last immunochemotherapy) or |

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|---|---|
| | 3. Relapsing / refractory BTK-inhibitors naïve MCL patients with measurable disease or bone marrow involvement revealed in trephine biopsy or<br>4. Patients fulfilling criteria 2 or 3, when ibrutinib therapy was initiated, responding to therapy<br>5. Patient qualified for allo SCT procedure by the transplant center participating in the trial with identified sibling donor or initiated Poltransplant search for matched unrelated donor.<br>6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1<br>7. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib and for 6 months after the transplant procedure if performed. Males who are sexually active must use highly effective methods of contraception during treatment and for 6 months after the transplant procedure if performed.<br>8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.<br>9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information. |
| **Exclusion Criteria:** | 1. Patients failing 5 or more previous therapy lines<br>2. Prior malignancy (or any other malignancy that requires active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 5 years<br>3. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or |

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| | any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (NYHA). Subjects with controlled, asymptomatic atrial fibrillation during screening can enroll on study.<br>4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.<br>5. Impaired hepatic function (as indicated by any of the following):<br>a. Serum total bilirubin > 2.5 x upper limit of normal (ULN)<br>b. Alanine amino transferase and/or aspartate amino transferase > 2.5 x ULN<br>c. Alkaline phosphatase > 2.5 x ULN<br>6. Impaired renal function: serum creatinine > 2.5 x ULN<br>7. Other concurrent serious diseases that increase Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) > 4<br>8. Central nervous system involvement with CLL<br>9. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components).<br>10. Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease).<br>11. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).<br>12. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.<br>13. Requiring or receiving a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer (see appendix 3 for a complete list) |

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| | 14. Requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.<br>15. Requiring proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.<br>16. Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) > 2x ULN.<br>17. History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.<br>18. Major surgical procedure within 30 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.<br>19. Known history of infection with HIV or any active uncontrolled systemic infection<br>20. Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded.<br>Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.<br>21. ANC < 500/µl, Platelets < 20 000/µl, and hemoglobin < 8 g/dl<br>22. Breastfeeding or pregnant.<br>23. Concurrent participation in another therapeutic clinical trial. |

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| **Dose Regimen/Route of Administration:** | Acalabrutinib is provided as hard 100 mg gelatin capsules for oral administration approximately every 12 hours. |
| **Concomitant Medications:** | **Prohibited Concomitant Therapy**<br>• strong cytochrome P450 3A4 (CYP3A4) inhibitors/inducers<br>• any protein pomp inhibitors, any vitamin K antagonists or any other anti-cancer medications, excluding used in transplant conditioning |
| **Study duration:** | **01.03.2019-31.10.2022** |

## 1.0 BACKGROUND INFORMATION

### 1.1 R/R CLL AND MCL

Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in adults in western societies with a year incidence of–4.8 - 5/100 000 [1] [2]. Clinical course of CLL is highly heterogeneous, indolent in some patients, while aggressive with resistance to the therapy and short overall survival in the others. Poor prognosis in patients with CLL is associated with the presence of 17p deletion/TP53 mutation or/and short response (less than 24 – 36 months) to immunochemotherapy [3]. The clinical importance of 17p deletion/TP53 mutation is associated with chemo-refractoriness [4]. As the results of CLL8 study shown, in patients treated with FCR protocol (fludarabine, cyclophosphamide, rituximab) as the first line therapy, progression-free survival (PFS) was only 11.3 months and overall survival (OS) was 33 months as compared to 56.8 and not reached in the whole patients group [5] [6]. Significant improvement in the outcome of patients with 17p del/TP53 mutation came with the introduction of the novel small molecule agents into CLL therapy, such as B-cell receptor inhibitors (BCRi), such as ibrutinib, Bruton Tyrosine Kinase (BTK) inhibitor and idelalisib, phosphoinositide 3-kinase (PI3K) delta inhibitor and Bcl-2 antagonist (venetoclax). In relapsed/refractory patients with 17p deletion treated with ibrutinib PFS median was up to 26 – 40 months and OS up to 57 months Ibrutinib is reimbursed in Poland in this patients group. Idelalisib is also an efficient option in these patients [7], however with higher toxicity (pneumonitis, colitis, transaminasemia, infections) [8], it is not reimbursed in Poland. BCRi therapy is also efficient in heavily pretreated fludarabine refractory patients [9] [10]. Though BCRi treatment altered the therapeutic landscape of CLL, the disease cannot be cured with small molecules that allow to maintain disease control without inducing deep response since partial response is observed in most patients. After four-year follow-up, CLL progression is observed in about 19% of patients treated with ibrutinib [11]. The preferred therapeutical option for this group is venetoclax that results in response in 70% of patients progressing during ibrutinib therapy [12]. Median PFS in patients treated with venetoclax after BCRi failure was not reached, in contrast to immunochemotherapy where it is was only 5 months [13]. Venetoclax is not reimbursed in Poland. Moreover, the optimal therapeutic option for patients with CLL progression on venetoclax is not established. That is why allogeneic stem cell transplantation, that offers a curative option and has the potential to improve the natural course of poor-risk CLL should be considered in patients with high-risk disease,

even in the era of novel therapies [14]. The concern for fully myeloablative allo-SCT in CLL is high toxicity and treatment related mortality (TRM). This is significantly lower when reduced-intensity conditioning (RIC) which is used that is currently recommended in CLL [15]. The efficacy of RIC allo-SCT is resonated by the T cell-mediated graft-versus leukemia effect that could eliminate the leukemic clone (usually over a period of 3-6 months) [16]. Event-free survival (EFS) five years after RIC allo-SCT was 35% – 45% and OS 50-70% confirming the curative potential but showing also the need for improvement. We hypothesize that acalabrutinib could be used both for bridging to alloSCT and after the procedure to augment disease control. Ibrutinib was shown to be effective before alloSCT and did not appear to adversely affect engraftment, GVHD risk, and NRM as reported by the Chronic Malignancy and the Lymphoma Working Parties of the EBMT (European Group of Blood and Bone Marrow Transplantation). Treatment with ibrutinib in patients relapsed after alloSCT resulted in minimal residual disease eradication in 36% of patients [17]. Moreover, ibrutinib was approved by the FDA for the treatment of adult patients with chronic GvHD, as it reduces severity of chronic GvHD symptoms in patients refractory to prior GvHD treatment [18]. These data suggest that using BCR inhibitors in patients after alloSCT could improve the outcome of patients with high-risk CLL. There is one ongoing clinical study with ibrutinib used before and after transplantation [NCT02869633]. There is so far no data on acalabrutinib in this setting.

Mantle cell lymphoma (MCL) is a relatively rare subtype of NHL with an incidence of 0.5 cases per 100,000 person-years, a male-to-female ratio of 2.3-2.5:1, and a median age at diagnosis of close to 70 years [19]. The relatively early development of resistance to immune-chemotherapy implies the necessity of therapy intensification already in the first line approach, including wherever possible intermediate cytarabine doses followed by autologous stem cell consolidation (ASCT) and rituximab maintenance [20]. Prognosis of MCL patients relapsing/ refractory to the first line therapy is poor. Although acalabrutinib increases RR and PFS compared to Ibrutinib in R/R MCL [21], majority of the patients will develop resistance to any subsequent regimens [22]. Therefore, offering an allogeneic transplant procedure to patients responding to BTK inhibitors, is fully justified, as it may be potentially curative.

### 1.2 BRUTON TYROSINE KINASE INHIBITION IN CLL AND MCL

Bruton tyrosine kinase (BTK) is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B-cells, myeloid cells, mast

cells, and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Khan 2001, Mohamed 2009, Bradshaw 2010). Bruton tyrosine kinase (BTK) is a key component of the signalosome that forms as part of the BCR pathway cascade, and is critical for the transduction and amplification of signals from the BCR (Figure 1.2) [23] [24]. When antigen binds the membrane immunoglobulin portion of the BCR, the resulting conformational change induces phosphorylation of the immunoreceptor tyrosine-based action motifs, causing the recruitment of BTK and other signalosome components. BTK is named after the pediatrician Ogden Bruton, who first described a case of X-linked agammaglobulinemia, a primary immunodeficiency that has since been linked to mutations in the BTK gene [25]. The essential role of BTK in MCL cell activation, proliferation and survival makes its inhibition a compelling therapeutic strategy.

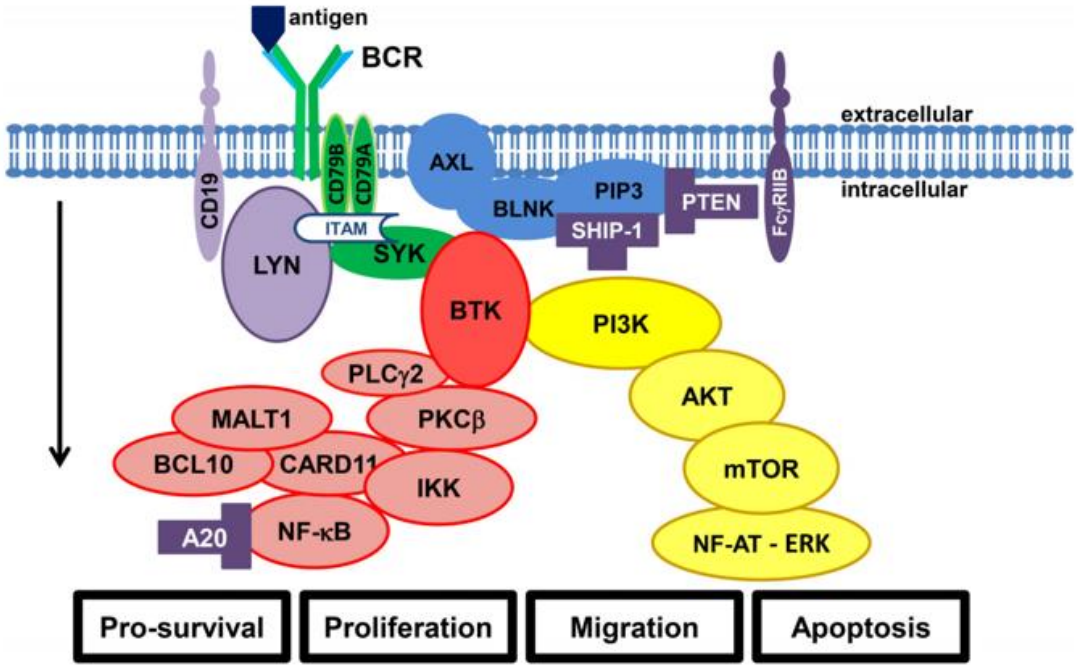


Figure 1-2 BCR signaling pathway

### 1.3 ACALABRUTINIB (ACP-196)

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally bioavailable in humans and is suitable for formulating in capsules.

Acalabrutinib is approved in the US for the treatment of adult patients with MCL who have received at least 1 prior therapy. It is also being evaluated for the treatment of patients with other B-cell malignancies.

### 1.3.1 Mechanism of Action

Acalabrutinib is a potent inhibitor of BTK in vitro and in vivo. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib [26]. Functional inhibition of non-target cells (e.g., T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

### 1.3.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator's Brochure.

### 1.3.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator's Brochure. Please refer to Section "Concomitant Therapy" for guidance on drugs that may cause drug-drug interactions.

## 1.4 CLINICAL EXPERIENCE – ACALABRUTINIB

For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator's Brochure.

### 1.4.1 Clinical Efficacy in CLL and MCL

Acalabrutinib is a highly selective, potent inhibitor of BTK [27] [28]. Acalabrutinib has a butynamide moiety that covalently binds Cys-481 in the ATP binding pocket of BTK, thereby blocking BCR signaling through BTK [26]. The US Food and Drug Administration (FDA) granted accelerated approval to acalabrutinib on October 31, 2017 for the treatment of patients with MCL who have received at least one prior therapy [21]. Acalabrutinib is also in clinical development for the treatment of other hematological malignancies, including chronic lymphocytic leukemia (CLL) and is included in the US National Comprehensive Cancer Network (NCCN) guidelines as a treatment option for

relapsed or refractory CLL. For further details please refer to section 5.3.1 of the Investigator's Brochure.

### 1.4.2 Adverse Events

There are no data on Acalabrutinib safety in the post-transplant patients. An aggregate safety analysis of acalabrutinib monotherapy was conducted in order to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. The analysis was performed on a 7-study integrated monotherapy population 'INT-7', which consisted of treated subjects in 5 acalabrutinib monotherapy studies (15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-004, ACE-WM-001) and treated subjects in the acalabrutinib monotherapy treatment arms of 2 additional combination studies (ACE-LY-003 and ACE-MY-001). As of the 03 September 2017 data extraction date, the pooled INT-7 population represented 614 acalabrutinib-exposed subjects with a median exposure of 21.9 months (range, 0.03 to 42.4 months). Overall, the safety of monotherapy acalabrutinib in subjects with hematologic malignancies has been acceptable in the integrated analysis. An overview of AEs for this population is presented in Table 1.4.2..

**Table 1.4.2. Overview of treatment-emergent adverse events of the INT-7 All Monotherapy Population**

| Adverse Event Category | N=614<br>n (%) |
|---|---|
| Any treatment-emergent adverse events | |
| Any grade | 609 (99.2) |
| Grade ≥3 | 334 (54.4) |
| Any adverse event related to acalabrutinib | |
| Any grade | 459 (74.8) |
| Grade ≥3 | 128 (20.8) |
| Any serious adverse events | 256 (41.7) |
| Adverse events leading to study drug discontinuation | 44 (7.2) |
| Grade 5 (fatal) adverse event | 27 (4.4) |

INT-7 studies include 15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001.

Note: A subject with multiple severity grades for a given adverse event was counted once under the maximum severity.

Data as of 03 Sep 2017.

Almost all subjects (609 [99.2%]) had at least 1 AE, and about half (334 [54.4%]) had at least 1 Grade ≥3 AE. The most commonly reported AEs of any grade were headache (42.3%), diarrhea (40.4%), fatigue (24.6%), nausea (23.6%), contusion (23.5%), cough (22.1%), and upper respiratory tract infection (21.7). The most frequently reported Grade ≥3 AEs were neutropenia (10.4%), anemia (7.5%), pneumonia (6.5%), thrombocytopenia (3.7%), and hypertension (3.1%).

Treatment-related AEs were reported for 459 (74.8%) subjects, and 128 (20.8%) subjects had Grade ≥3 treatment-related AEs. The most frequently reported treatment-related AEs of any grade were headache (29.5%), diarrhea (17.4%), contusion (14.5%), nausea (9.3%), fatigue (7.5%), petechiae (7.5%), neutropenia (7.0%), arthralgia (5.9%), and dizziness (5.0%). The most frequently reported treatment-related Grade ≥3 AEs was neutropenia (6.8%).

### 1.4.3 Warnings and Precautions

#### 1.4.3.1 Hemorrhage

Serious hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with acalabrutinib; some of these bleeding events resulted in fatal outcomes. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding.

#### 1.4.3.2 Infection

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have been reported in clinical studies with acalabrutinib. The most frequently reported Grade 3 or 4 infection was pneumonia. Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation (resulting in liver failure and

death in 1 case) and cases of progressive multifocal leukoencephalopathy have occurred in subjects with hematologic malignancies. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

#### 1.4.3.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects should be closely monitored as appropriate.

#### 1.4.3.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer. Advise protection from sun exposure.

#### 1.4.3.5 Atrial Fibrillation

Events of atrial fibrillation/flutter have been reported in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation.

The mechanism for atrial fibrillation is not well understood.

## 2.0 STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVE:

- Safety:
  - adverse event (AE) incidence
  - serious adverse event (SAE) incidence
- Response to therapy:
  - partial and complete remission rate (PR and CR),
  - minimum residual disease CR (MRD CR) rate assessed by flow cytometry in peripheral blood (PB) and bone marrow (BM)

### 2.2 SECONDARY OBJECTIVE(S):

- relapse incidence (RI),
- non-relapse mortality (NRM),
- progression free survival (PFS),
- overall survival (OS),

### 2.3 EXPLORATORY OBJECTIVE(S)

- acute and chronic graft versus host disease (GvHD) incidence,
- GvHD-free and relapse-free survival (GRFS), cytometric assessment of immune cell populations: T cell subsets (CD4+ T cells, CD8+ T cells, Th1, Th2, Th17, T regulatory cells), NK cells, NKT cells and normal B cells, B-regulatory cells

## 3.0 STUDY DESIGN

In this phase II multicenter trial we plan to use acalabrutinib before and after allogeneic hematopoietic stem cell transplantation (alloSCT) with reduced intensity conditioning (RIC) in patients with refractory/relapsed MCL and CLL with poor prognostic factors. Acalabrutinib will be used before alloSCT with the intention to reduce tumor burden and after transplant to augment disease control. Since chronic GvHD is mediated by activated B lymphocytes, we also speculate that the drug as a BTK inhibitor may reduce the severity and incidence of chronic graft-versus-host disease (GvHD) after alloSCT, as it was shown for ibrutinib.

Feasibility and safety issues will be the primary target of this small trial (25 transplanted pts). TEAE and SAE of acalabrutinib in patients after alloSCT that was not previously assessed.

We hypothesize that this treatment will improve the efficacy of the alloSCT – this issue will be addressed by serial minimal residual disease (MRD) evaluation in peripheral blood and bone marrow. This treatment strategy could significantly improve the outcome of poor prognosis MCL and CLL patients. The study schema is provided below (Figure 3-1).

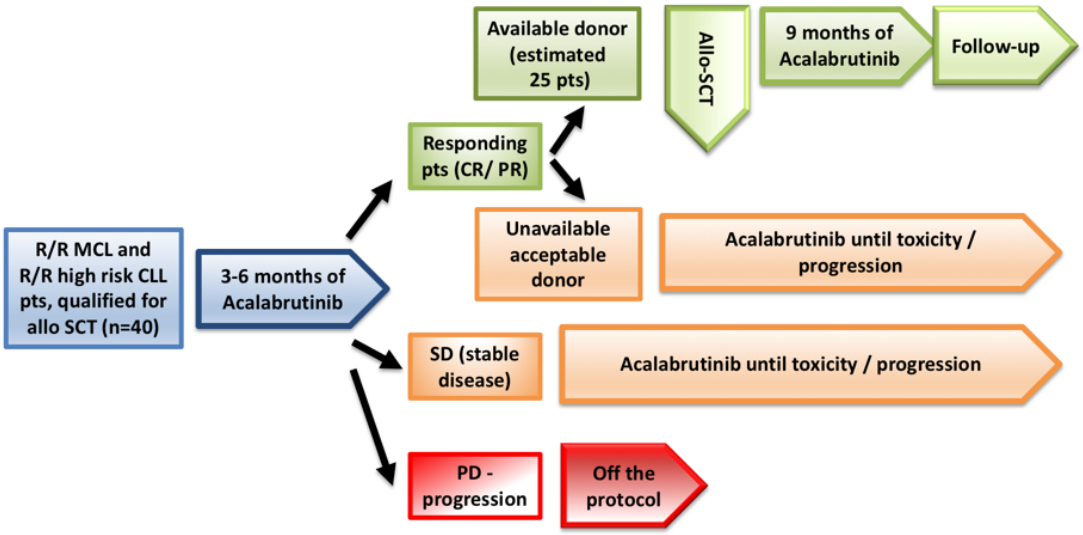


Figure 3-1. Study Schema

## 3.1 STUDY PARAMETERS

### 3.1.1 Efficacy Parameters

Partial and complete remission rate (PR and CR) will be assessed, based on medical history, clinical examination, laboratory assessment and imaging studies. Assessments will be done at the study entry, before the transplant and subsequently 1, 3, 6 & 9, 12, 15 and 18 months after allo SCT procedure. Imaging studies will be done on the study entry, at 3 months, before the transplant if Acalabrutinib was administered for more than 3 months, on re-initiating of acalabrutinib (which is 1-3 months after the transplant), at the end of post - transplant acalabrutinib therapy, 18 months after the transplant and any time when investigator will suspect PD. In Patients who would not be transplanted imaging studies will be performed on the study entry, at 3 months, at 6 months, and later any time when investigator will have suspect PD.

Response in CLL and MCL patients is defined according to the standard IWCLL criteria updated in 2018 [29] and Cheson Criteria [30] [31] respectively. Additionally, for the purpose of the protocol in PR patients the maximal diameter of lymph nodes < 5 cm is required, since lymphadenopathy ≥ 5 cm was recognized as a major predictor in relapse in CLL patients treated with ASCT after nonmyeloablative conditioning [32].

Imaging studies will be based on CT scans.

Additionally, minimum residual disease CR (MRD CR) rate will be assessed by flow cytometry. In this study, we plan to evaluate MRD using flow cytometry (FCM), first in peripheral blood (PB) and in case of negativity in bone marrow (BM) in a central laboratory certified for MRD assessment at the following time points: will be performed at the study entry, before the transplant and subsequently 1, 3, 6 & 9, 12, 15 and 18 months after allo SCT procedure.

Relapse incidence (RI), non-relapse mortality (NRM), progression free survival (PFS), and overall survival (OS) are regarded as secondary targets and will be based on local investigators assessment.

### 3.1.2 Safety Parameters

The safety of acalabrutinib will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation of study treatment or death.

For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 or higher. Standard definitions for seriousness will be applied (see Section 6.1).

### 3.1.3 Exploratory Parameters

Since the incidence and severity of GvHD may be altered by acalabrutinib usage, acute and chronic graft versus host disease (GvHD) incidence and GvHD-free and relapse-free survival (GRFS) are regarded as exploratory parameters. hey will be assessed according to Statistical Guidelines for EBMT by M. Labopin and S. Iaobelli and GRFS definition according to Holtan et al [33].

Donor chimerism analysis will be routinely performed at 1, 3, 6, 9 and 12 months post-alloSCT on peripheral blood; then every 3 months during follow-up period. For patients with progressive mixed chimerism confirmed on 2 subsequent tests done 2 weeks apart

the intervention will consist of calcineurin inhibitor (CI) taper. For patients with relapse or decreasing donor chimerism DLI is allowed as per institutional protocol. Chimerism analysis will be routinely performed (for time-points see the table) at the local labs.

Evaluation of immune cell populations, at the study entry, at 3 months, 6 months, at the time of transplant, then every three months for the following 18 months using FCM, such as T cell subsets (CD4+ T cells, CD8+ T cells, Th1, Th2, Th17, T regulatory cells), NK cells, NKT cells and normal B cells, B-regulatory cells as well as immunoglobulin levels (IgG, IgA, IgM). (for time-points see the table).

Additionally, frozen cells for future assessment will be collected.

**Table 3.1.3. Summary of Study Assesments:**

| | Screening | Treatment period | | | | | | | | TT | SFU | FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before alloSCT | | | | | | At alloSCT | After alloSCT | | | |
| Study month | -1 - 0 | 1 | 2 | 3 | 4 | 5 | 6 | | 1,3,6,9 | | | 12,15,18 |
| Physical examination | x | x | x | x | x | x | x | x | x | x | x | x |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical history, including AE, SAE data collection | x | x | x | x | x | x | x | x | x | x | x | |
| Rai staging | x | | | | | | | | | | | |
| ECOG performance status | x | x | x | x | x | x | x | x | x | x | x | x |
| Vital signs (pulse, BP, temp.) | x | x | x | x | x | x | x | x | x | x | x | x |
| ECG | x | | | | | | | | | | | |
| Urine or serum pregnancy test | x | | | | | | | x | 12 months after alloSCT | | | |
| FBC | x | x | x | x | x | x | x | x | x | x | x | x |
| U&E and LFT[1] | x | x | x | x | x | x | x | x | x | x | x | |
| HBV, HCV, HIV serology[2] | x | | | | | | | | | | | |
| Serum immunoglobulins (IgG, IgM, IgA) | x | | | x | | | x | x | x | x | x | x |
| ß$_2$-microglobulin | x | | | | | | | | | | | |
| Coombs test | x | | | | | | | | | | | |
| Urine analysis | x | | | | | | | | | | | |
| FISH panel, p53 mutation status* | x | | | | | | | | | | | |
| IgVH mutation status* | x | | | | | | | | | | | |
| Tumor evaluation (imaging studies) | x | | | x | | | x | x | see 3.1.1 for details | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MRD assessment by flow cytometry* | x | | | x | | | x | x | x | | | x |
| Chimerism | | | | | | | | | Until full donor chimerism | | | |
| Immune parameters evaluation by flow cytometry* | x | | | x | | | x | x | x | | | x |
| Blood samples for additional assessments | x | | | x | | | x | x | x | | | x |

TT, treatment termination visit (within 7 days of the last dose of study drug); SFU, safety follow-up visit (30+/-7 days the last dose of study drug), FU, follow-up visits

(*) – procedures performed by the central lab.

(1) – U&E and LFT include: calcium, chloride magnesium, phosphate/phosphorus, potassium, sodium ALT, AST, total bilirubin albumin, alkaline phosphatase, , bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, lactate dehydrogenase (LDH),total protein, and uric acid.

(2) – hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody

## 3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

According to current guidelines of European Society of Medical Oncology (ESMO), in CLL patients with 17p deletion/TP53 mutation as well as in the patients with refractory CLL or short remission BCR inhibitors are recommended as preferred therapy. Venetoclax is recommended in patients who are unsuitable to BCRi or after BCRi failure. In both groups of patients, allogeneic stem cell transplantation should be considered [ESMO]. Options for R/R patients with MCL are even more limited. Although both ibrutinib and acalabrutinib are registered in this setting, PFS is moderate and the therapy for BTK inhibitor resistant patients is an undisputable unmet medical need. We

hypothesize that acalabrutinib might be efficient treatment reducing tumor burden before alloSCT and used after the transplantation might improve the results of the procedure, both in terms of disease control and influence on GvHD incidence The rationale for this hypothesis are the clinical data on ibrutinib. Acalabrutinib is a next generation more selective BTK inhibitor with promising safety and efficacy profiles in patients with relapsed CLL and MCL [27] [21]. There is no data on safety or efficacy of acalabrutinib in patients after alloSCT.

Disease status in patients with CLL/ MCL treated with acalabrutinib after alloSCT will be evaluated by MRD assessment. MRD negativity in CLL is defined as detection of less than one leukemic cell per 10 000 leukocytes in peripheral blood (PB) or bone marrow (BM) [29]. In patients treated for CLL, MRD negativity following therapy was shown to be a strong independent predictor for PFS and OS irrespective of the type and line of treatment, achievement of CR and pre-treatment patients characteristics [34]. What is more, MRD negativity was found to have a higher prognostic value than achievement of complete clinical response (CR) [35]. In patients with CLL undergoing alloSCT, MRD negativity 12 months after transplantation was associated with significantly longer event-free survival (EFS), PFS and OS [36] [37]. MRD eradication can be achieved several months after alloSCT, probably because the onset of graft-versus-leukemia effect is not immediate. It has been suggested that kinetics rather than a single MRD assessment is more meaningful. Elimination of MRD in BM has higher negative predictive value for predicting subsequent relapse risk than in PB. Therefore, for treatment delivered with curative intent, like allo-SCT, it would be likely essential to evaluate MRD in BM. According to EMA guidelines MRD status should be determined around 3 months after the end of therapy and patients should be first screened for eradication in PB and if negativity is shown, this should be confirmed in BM [www.ema.europa.eu]. Evaluation of MRD is currently not recommended for routine clinical practice, but is considered as an important endpoint surrogate for PFS in clinical trials [1] where both PR and CR should be categorized as MRD+ or MRD- [38]. Standardized protocols of MRD evaluation in CLL with sensitivity of ≥ $4x10^{-4}$ are either multiparameter (four-color or more) flow cytometry (FCM) or allele- specific oligonucleotide PCR [39]. There is no specific method to be used as both are considered as appropriate.

MRD monitoring in MCL patients will be adapted according to European MCL Network (EMCLN) experience [40].

## 3.3 SELECTION OF STUDY POPULATION

### 3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. Relapsing / refractory BTK-inhibitors naïve CLL patients meeting IWCCL criteria for requiring treatment:
    a. after 1-4 therapy lines if del 17 or p53 mutation in >10% of analyzed CLL cells (PB or BM) or
    b. after 2-4 therapy lines if high risk CLL (refractory or less than 24 months response to the last immunochemotherapy) or
3. Relapsing / refractory BTK-inhibitors naïve MCL patients with measurable disease or bone marrow involvement revealed in trephine biopsy or
4. Patients fulfilling criteria 2 or 3, when ibrutinib therapy was initiated, responding to therapy
5. Patient qualified for allo SCT procedure by the transplant center participating in the trial with identified sibling donor or initiated Poltransplant search for matched unrelated donor.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib and for 6 months after the transplant procedure if performed. Males who are sexually active must use highly effective methods of contraception during treatment and for 6 months after the transplant procedure if performed.
8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.

9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

### 3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Patients failing 5 or more previous therapy lines
2. Prior malignancy (or any other malignancy that requires active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 5 years
3. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening. Subjects with controlled, asymptomatic atrial fibrillation during screening can enroll on study.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
5. Impaired hepatic function (as indicated by any of the following):
    a. Serum total bilirubin > 2.5 x upper limit of normal (ULN)
    b. Alanine amino transferase and/or aspartate amino transferase > 2.5 x ULN
    c. Alkaline phosphatase > 2.5 x ULN
6. Impaired renal function: serum creatinine > 2.5 x ULN
7. Other concurrent serious diseases that increase Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) > 4
8. Central nervous system involvement with CLL
9. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components).

10. Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease).
11. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
12. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
13. Requiring or receiving a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer (see appendix 3 for a complete list)
14. Requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
15. Requiring proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
16. Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) > 2x ULN.
17. History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
18. Major surgical procedure within 7 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
19. Known history of infection with HIV or any active uncontrolled systemic infection
20. Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.
21. ANC < 500/µl, Platelets < 20 000/µl, and hemoglobin < 8 g/dl
22. Breastfeeding or pregnant.
23. Concurrent participation in another therapeutic clinical trial.

### 3.3.3 Enrollment Procedures

After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be enrolled into the study.

## 3.4 STUDY DRUG

### 3.4.1 Premedication

No specific premedication or supporting medications are required in conjunction with acalabrutinib administration.

### 3.4.2 Formulation, Packaging, and Storage

**Acalabrutinib,** the investigational product, acalabrutinib capsules for oral administration, is supplied as yellow and blue, opaque hard gelatin capsules, with 100 mg of acalabrutinib as the active ingredient. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide and indigotine (FD&C Blue 2).

Acalabrutinib will be provided in white, high-density polyethylene bottles.

Refer to the acalabrutinib Investigator's Brochure for additional information regarding the drug product to be used in this trial.

### 3.4.3 Administration of Study Drug

Acalabrutinib capsule is administered BID and taken orally approximately every 12 hours. The capsules should be swallowed intact with water. Subjects should not attempt to open capsules or dissolve them in water. Acalabrutinib can be taken with or without food.

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 3.9.2.

### 3.5 STUDY TREATMENT SCHEDULE

Acalabrutinib 100 mg will be administered orally twice daily, every day (for details and explanations see below).

### 3.6 DURATION OF THERAPY

Acalabrutinib will be administered for 3-6 months before the intended alloSCT. Patients with CR or PR (defined by Cheson and IWCLL criteria + limfadenpathy < 5 cm) after initial BTK inhibitor will proceed to alloSCT, donor availability and their general status permitting. After **r**estarting acalabrutinib after the transplant procedure (see details below) it will be administered for further 9 months. In patients who do not have an acceptable donor acalabrutinib will be administered until disease progression or unacceptable toxicity.

Post-HSCT acalabrutinib treatment initiation
Acalabrutinib will be initiated 30-90 days after (*) the procedure for 9 months in patients who will fulfill the following criteria:

- ANC ≥ 1000/µl and platelet count ≥ 50 000/µl
- ECOG 0-2
- adequate renal function: serum creatinine < 2 x ULN OR creatinine clearance (calculated clearance permitted) ≥ 40 mL/min
- total bilirubin =< 2.5 x upper limit of normal (ULN)
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) =< 2.5 x upper limit of normal (ULN)

Patients can not have:

- active systemic infection
- active uncontrolled grade 3-4 gastrointestinal or liver acute GvHD
- any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety after HSCT
- clinically significant active bleeding

Acalabrutinib will be continued for 9 months in the absence of disease progression, worsening symptoms of GvHD or unacceptable toxicity.
(*) – Acalabrutinib may be re-started earlier after the transplant if patients do not achieve clinical CR or experience early progression after the transplant

### 3.7 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences a treatment-related toxicity or other intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree.

Dose modifications for the following treatment-emergent toxicities are provided in Table 3-X:

- Grade 4 neutropenia (< 500/μL) for > 7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2006] and use must be recorded on the case report form [CRF]).
- Grade 3 thrombocytopenia in presence of significant bleeding.
- Grade 4 thrombocytopenia.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- any Grade 4 active systemic infection or unmanageable G3 (including, among the others CMV and EBV)
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

**Table 3-7: Drug Modification Actions for Acalabrutinib**

| Occurrence | Action |
|---|---|
| 1st – 2nd | Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level |
| 3rd | Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (100 mg QD) |
| 4th | Discontinue acalabrutinib |

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade ≤ 1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the AE resolves to Grade ≤1 or if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. The maximum dose of acalabrutinib is 100 mg BID. Any other clinically important events where dose delays may be considered appropriate must be discussed with the Principal Investigator.

## 3.8 CONCOMITANT THERAPY

### 3.8.1 Permitted Concomitant Therapy

**Transplant procedure:**

A. Acceptable donors:

- HLA-identical sibling
- HLA matched (HLA-A, -B, -C, -DR, -DQ i.e. 10/10) unrelated donor
- Unrelated donor with single HLA mismatch
- Haploidentical family donor

B. Source of stem cell

- For alloSCT from HLA-identical sibling or HLA matched (10/10 or 9/10) unrelated donor: preferably PBSC 4-6 x $10/^{6}$ CD34+/kg recipient's body weight.
- For HSCT from haploidentical donors: according to institutional protocol

C. Conditioning before alloSCT from HLA-identical sibling or matched (10/10 or 9/10) unrelated donor. Investigators may choose to use reduced intensity conditioning based on either bendamustine or TBI, both in combination with fludarabine and rituximab

BFR:

- Bendamustine 130 mg/$m^2$ infused iv over 60 min daily on days −5 to − 3
- Fludarabine 30 mg/$m^2$ iv daily on days -5 to -3
- Rituximab 375 mg/$m^2$ iv on day -6

TBI/F/R:

- Fludarabine 30 mg/$m^2$ i.v. daily on days -5 to -3
- TBI 4 Gy on day -1 or 0
- Rituximab 375 mg/$m^2$ iv on day -6

D. Conditioning before HSCT from haploidentical family donors

- Cyclophosphamide 14.5 mg/kg i.v.daily on days -6 and -5
- Fludarabine 30mg/m2 i.v.daily on days -6, -5, -4, -3 and -2
- TBI 2 Gy on day -1

**GvHD prophylaxis:**

A. For alloSCT from HLA-matched sibling donor

- Tacrolimus iv/po or CSA iv/po starting on day -2 per institution standard
- MTX 10 mg/$m^2$ on day +1, 5 mg/$m^2$ iv on days +3, +6, optionally +11
- Rituximab 375 mg/$m^2$* i.v on day +1, +8

**Rituximab dose escalation to 500 mg/$m^2$ is allowed

Tacrolimus/CSA taper will be initiated at +100 - +180 days after alloSCT in patients with no active GvHD. Tacrolimus/CSA doses wil be tapered earlier and more rapidly in patients with persistent/progressive disease and no GvHD.

B. For alloSCT from HLA-matched (10/10 or 9/10) unrelated donor

- ATG: Thymoglobuline 1.5 mg/kg daily i.v. on days -2, -1 (total dose 3.0 mg /kg) or ATG Neovi (Fresenius) 10 mg/kg i.v. daily on days -2, -1
- Tacrolimus iv or p.o. or CSA iv or p.o.starting on day -2
- MTX 10 mg/m$^2$ i.v. on day +1, 5 mg/m2 p.o. on days +3, +6, +11
- Rituximab 375 mg/m$^2$ iv on days +1 and +8

*Rituximab dose escalation to 500 mg/m$^2$ is allowed

Tacrolimus/CSA taper will be initiated at +100 - +180 days after alloSCT in patients with no active GvHD. Tacrolimus/CSA doses will be tapered earlier and more rapidly in patients with persistent/progressive disease and no GvHD.

C. For HSCT from family haploidentical donor or optionally for alloSCT from HLA-mismatched (9/10, except for mismatch regarding HLA-DQB1) unrelated donor

- Cyclophosphamide 50 mg/kg i.v. on days +3, +4
- Tacrolimus p.o. or i.v. starting on day +5
- Mycophenolate mofetil 3 x 15 mg/kg p.o. or i.v. on days from +5 to +35

Tacrolimus taper will be initiated at +120 - +150 days after alloSCT and should be tapered off by day +150- +180 days after alloSCT in patients with no active GvHD. Tacrolimus doses will be tapered more rapidly in patients with persistent/progressive disease and no GvHD.

**Supportive care:**

Patients will receive supportive care with antibiotics, antifungals, antivirals and immunizations after alloSCT according to institutional guidelines

### 3.8.2 Prohibited or Restricted Concomitant Therapy

Any (other than mentioned in 3.8.1) chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited.

Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited.

The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 3) should be avoided when possible (see Section 3.9.2). If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. For additional information on drugs with potential drug-drug interactions, refer to Section 3.9.2.

## 3.9 PRECAUTIONS

### 3.9.1 Dietary Restrictions

Acalabrutinib can be taken with or without food.

### 3.9.2 Drug-drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated.

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin decrease acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 3) should be avoided when possible.

If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A4 while on study, the subject should be monitored closely for any potential toxicities.

The effect of agents that reduce gastric acidity (eg, proton pump inhibitors or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole

or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

### 3.9.3 Reproductive Toxicity

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown.

For results of acalabrutinib nonclinical reproductive toxicity studies, including definitive embryofetal development studies, please refer to the Investigator's Brochure.

Women of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception throw-out the trial and 6 months after the last dose of BTK inhibitor. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required. Please refer to the Investigator's Brochure for detailed definitions for WOCBP and highly effective methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.2.4.

### 3.9.4 Overdose Instructions

Clinical information relevant to overdose is not available. For results from nonclinical overdose studies in rats and dogs, please refer to the Investigator's Brochure.

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF and reported to Sponsor under the same timelines as an SAE.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF. If the associated AE fulfills serious criteria, Investigators should report the event to the Sponsor within 24 hours using the SAE Reporting Form. The Sponsor should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta-Pharma per contractual guidelines.

In the event of subject ingestion of more than the recommended acalabrutinib dosage, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

### 3.10 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

The investigator may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from the study at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the investigator.
- Any subject who starts new chemotherapy or chemoimmunotherapy for the treatment of disease being studied, becomes pregnant or breastfeeding, is significantly noncompliant, should be withdrawn from study treatment.

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted.

### 3.11 REMOVAL FROM STUDY

Reasons for removal of a subject from the study are:

- Subject's withdrawal of consent from study
- Decision by sponsor
- Subject lost to follow-up
- Death

### 3.12 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the Sponsor's Pharmacovigilance procedures. Adverse events, AESIs, and SAEs will be reviewed internally as part of ongoing safety surveillance.

Quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths).

## 4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 1. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

### 4.1 DESCRIPTION OF PROCEDURES

#### 4.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information, if required by local regulations. A copy of the informed consent form, including patient's signature, will be provided by the investigator to the patient. If the amendment to the

protocol substantially alters the trial design or the potential risks to the patients, the patient's consent to continue participation in the trial must be obtained.

### 4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview performed at screening. Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

### 4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. Important additional requirements for reporting SAEs are explained in Section 6.2.

### 4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug.

### 4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3.3. All screening procedures, unless otherwise indicated, should be completed within 8 days of the first dose of study drug.

### 4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 2.

### 4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous

system, and lymphatic system. As a part of the tumor assessment, a full physical examination should be performed to assess the extent of disease involvement. The exam should also include the evaluation of presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Vital signs (blood pressure, pulse, and body temperature) will be assessed after the subject has rested in the sitting position for at least 5 minutes.

#### 4.1.8 Electrocardiogram

12-lead electrocardiogram (ECG) is required in all patients at screening and from then when clinically indicated. Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs. Include study specific schedule for ECGs.

#### 4.1.9 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential.

All women of childbearing potential will have a serum or urine pregnancy test at screening, 14 days prior first dosing, at transplant and at the end of acalabrutinib exposure and at specified subsequent visits. Positive urine pregnancy test should be confirmed by serum test.

#### 4.1.10 Hematology

Hematology studies must include complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and absolute lymphocyte count (ALC).

#### 4.1.11 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

### 4.1.12 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see Appendix 1 and exclusion criterions #20).

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter as per institutional practices. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels).

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during screening

### 4.1.13 Additional clinical tests or procedures

- Quantitative immunoglobulins (IgG, IgA and IgM) should be evaluated at the study entry and then every 3 months
- Coombs test (indirect and direct) should be performed at screening and repeated if necessary
- $B_2$-microglobulin should be evaluated at the study entry
- Molecular cytogenetics FISH (17p-deletion, 13q deletion, trisomy 12) and p53 mutation analysis (TP53 mutation) at screening and at progression

Patients must have documented B-CLL according the NCI criteria. B-CLL cells co-express the T-cell antigen CD5 and B-cell antigen (CD20 and CD23). The levels of surface immunoglobulins (sIg, CD20 and CD79b are characteristically low compared with those found on normal C-cells. Each B-cell is monoclonal with regard to expression of either κ or λ.

### 4.1.14 Biomarker Studies

Blood samples will be used for further characterization of circulating tumor cells, lymphocyte and myeloid cell subsets.

Evaluation of immune cell populations, at the study entry, at 3 months, at the time of transplant, then every three months for the following 18 using FCM, such as T cell subsets (CD4+ T cells, CD8+ T cells, Th1, Th2, Th17, T regulatory cells), NK cells, NKT cells and normal B cells, B-regulatory cells as well as immunoglobulin levels (IgG, IgA, IgM). (for time-points see the table Appendix 1)

MRD using FCM, first in PB and in case of its negativity in BM in a laboratory certified for MRD assessment (for time-points see the table, BM analysis if required should be performed together with PB analysis at the next scheduled patient visit)

Chimerism analysis will be routinely performed (for time-points see the table in Appendix 1) at the local labs. Additional exploratory studies may include somatic mutation in IgVH and IgVH3-21 usage in previously untreated population.

### 4.1.15 Tumor Assessments

A pretreatment computerized tomography (CT) scan with contrast (unless contraindicated) is required of the neck, chest, abdomen, and pelvis and any other disease sites within 30 days before the first dose of study drug.

On-treatment CT scans with contrast (unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites will be done for tumor assessments every 3 months (± 10 days) until 18$^{th}$ month after alloSCT, or more frequently at investigator discretion. At all other visits, tumor assessments will be done by physical exam and laboratory results.

In patients with severe renal insufficiency at screening use CT contrast according to local practice. If necessary, use MRI scan. CT without contrast is not recommended except for patients who develop renal insufficiency during treatment. It is obligatory to use the same imaging technique for all tumor evaluation.

When progressive disease is detected by physical examination in the absence of any objective hematological progression, a CT scan of involved nodes will be performed. In

addition, CT scans may be performed at any time at the investigator discretion, if clinically indicated.

#### 4.1.16 Study Drug Accountability

See Section 7.5.

### 4.2 ASSESSMENT OF RESPONSE TO TREATMENT

Response assessments will be evaluated based on International Workshop on Chronic Lymphocytic Leukemia (IWCLL) and revised Cheson criteria for MCL for Treatment and Tumor Response Criteria (refer to Appendix 5).

### 4.3 TREATMENT TERMINATION AND SAFETY FOLLOW-UP VISITS

A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason, including disease progression. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit.

Each subject should be followed until the safety follow-up (SFU) visit at 30 (+ 7) days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. After TT there will be three follow-up visits at months +12, +15, +18. The Schedule of Assessments (Appendix 1) describes the procedures required for the TT, SFU and FU visits.

### 4.4 FOLLOW-UP FOR PROGRESSION AND SURVIVAL

#### 4.4.1 PFS as an Endpoint: Discontinuation Follow-up

Each subject should be followed until disease progression or the start of alternative anticancer therapy. If neither of these has occurred at the time of the 30-day SFU visit, discontinuation follow-up (DFU) visits should occur approximately every 3 months until disease progression or next anticancer treatment.

### 4.4.2 OS as an Endpoint: Long-term Follow-up

Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or lost to follow up.

## 4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

# 5.0 STATISTICAL METHODS OF ANALYSIS

## 5.1 GENERAL CONSIDERATIONS

This is a Phase 2, single-arm trial designed to assess the safety and efficacy of acalabrutinib in subjects with CLL and MCL undergoing allo SCT.

The severity of AEs (adverse events), TEAEs (treatment emerge adverse events) and SAEs (severe adverse events) will be described according to Common Terminology Criteria for Adverse Events (CTCAE v4.3 or higher).

An AE summary table will present the number of events, number of patients and the percentage of patients having AEs, SAEs, TEAEs and TEAEs that led to study discontinuation

Tabulation of summary statistics, graphical presentation and statistical analyses will be performed using appropriate statistical software. Continuous, quantitative variable summaries will include the number of patients (N) (with non-missing values/valid cases), mean and standard deviation.

Categorical, qualitative variable summaries will include the frequency and percentage of patients/entries, who/which are in particular categories.

The assumed overall type I error rate/significance level for the primary and secondary efficacy parameters is 5%, two-sided. Two-sided confidence limits will be evaluated at

95%, p-values from inferential tests comparing patient cohorts/patient subgroups will be compared to 5%.

Missing values will not be substituted by estimated values. All statistical evaluations will be based in valid cases except for procedures described for calculating response rates or in case of censoring within Kaplan-Meier methodology. In case of incomplete start or stop dates of AEs or concomitant medication appropriate conservative imputation methods will be specified in the statistical analysis plan (SAP).

Baseline values will be defined as the last pre-administration observation used for calculating post-administration changes from baseline.

## 5.2 RATIONALE FOR SAMPLE SIZE

Summing up, for our study the sample size is sufficient to reach the difference close to 20%-25% with statistical power between 80%-90% and alpha = 5%.

We used the article by Hern [41] containing sample size tables for phase II of clinical trials based on the exact binomial distribution. We decided to use it because the Fleming's procedure based on a normal approximation is technically incorrect for small clinical trials like ours. Table below shows the part of the table from [41] adequate for our study.

Table I. (Continued)

| $p_0$ | $p_1$ | $\alpha=0.05;\ 1-\beta=0.8$ | $\alpha=0.05;\ 1-\beta=0.9$ | $\alpha=0.01;\ 1-\beta=0.8$ | $\alpha=0.01;\ 1-\beta=0.9$ |
|---|---|---|---|---|---|
| 0.60 | 0.65 | 371/585 | 507/806 | 603/946 | 779/1230 |
| | 0.70 | 96/143 | 130/197 | 157/232 | 202/303 |
| | 0.75 | 44/62 | 59/85 | 74/103 | 90/128 |
| | 0.80 | 25/33 | 33/45 | 42/55 | 52/70 |
| | 0.85 | 17/21 | 21/27 | 26/32 | 33/42 |
| | 0.90 | 12/14 | 14/17 | 19/22 | 21/25 |
| | 0.95 | 9/10 | 9/10 | 13/14 | 16/18 |
| 0.65 | 0.70 | 373/545 | 519/764 | 612/890 | 793/1160 |
| | 0.75 | 96/133 | 128/180 | 157/216 | 201/280 |
| | 0.80 | 42/55 | 56/75 | 70/91 | 89/118 |
| | 0.85 | 25/31 | 33/42 | 40/49 | 50/63 |
| | 0.90 | 17/20 | 20/24 | 26/30 | 31/37 |
| | 0.95 | 11/12 | 14/16 | 15/16 | 19/21 |

In the table above $p_0$ is the highest level of efficacy (proportion in control group), $p_1$ – minimal required level of efficacy (proportion in the intervention group). The trial tests the null hypothesis $H_0$: $P \leq p_0$ against the alternative hypothesis $H_1$: $P \geq p_1$. Red box shows the proper lines. If we assume 20% difference in the response rate ($p_1$ = 80%) then we need 45 patient among whom 33 will be healthy after the treatment with alpha = 5% and statistical power = 90%. Higher difference e.g. 25% ($p_1$ = 85%) requires 27 patients in the trial with 21 patient healthy after the treatment (alpha = 5% and statistical power = 90%). The green box shows the sample size similar to our study (n = 35) with difference equal to 20% and alpha = 5% with statistical power = 80%.

## 5.3 ANALYSIS POPULATIONS

All efficacy and safety analysis will be performed using the treated population, which consists of all subjects who receive any amount of study treatment. The analysis of MRD negative CR will only include subjects who have achieved complete response.

## 5.4 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

## 5.5 ENDPOINT DATA ANALYSIS

### 5.5.1 Efficacy Endpoint(s)

The primary efficacy endpoints include overall response rate (ORR), complete response (CR) rate, and minimal residual disease (MRD) negative CR rate.
Secondary endpoints include relapse incidence (RI), non-relapse mortality (NRM), progression free survival (PFS), overall survival (OS), duration of response (DOR).

### 5.5.2 Safety Endpoint(s)

All safety variables will be analyzed for the safety population. The safety population includes all patients who will receive at least one dose of study medication. Incidence rates of AEs Grade $\geq$ 3 will be presented two-sided 95% Clopper Pearson Cis.
All AE will be assessed according to the NCI-CTCAE, v5.0 grading system.

AE will be summarized according to the primary system-organ class (SOC) and within each SOC.
AE grade 3 or higher, AEs related to acalabrutinib, AEs leading to treatment interruption or discontinuation, AEs of special interest and SAE will will be analyzed in a similar way to all AEs. Cause of death will be also summarized and listed.
The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. Discontinuation form the study will be also summarized and listed.
Descriptive statistics will be presented for cumulative study medication doses, dose modifications and duration of exposure.
ECG will be analyzed descriptively.
Laboratory parameters, hematology and serum chemistry will be presented in shift tables of NCI-CTCAE, V5.0 grade at baseline versus worst grade during treatment period. The summary of laboratory parameters, presented by means, standard deviation, maximum and minimum will be also presented. Selected laboratory parameters will be also graphically presented over time, including ALT, AST and bilirubin.
ECOG performance status will be summarized over time.

### 5.5.3 Exploratory Endpoints

Immune cell populations will be presented as percentages and absolute values. The summary of immune parameters, presented by means, standard deviation, maximum and minimum will be presented. Selected laboratory parameters will be also graphically presented over time. The Wilcoxon paired test will be used to compare the results before during and after therapy. The Spearman rank correlation coefficient will be used in correlation tests.
Cumulative incidence functions will be used to estimate aGvHD and cGvHD incidence in a competing risks setting, with death and relapse considered as competing events.
Descriptive statistics will be presented for donor chimerism evaluation.

### 5.5.4 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose delay, reductions and interruptions.

For each subject, acalabrutinib compliance will be described in terms of the proportion of study drug actually taken.

### 5.5.5 Analysis of Efficacy Parameters

Definitions for efficacy endpoints, are standard

#### 5.5.5.1 Primary Efficacy Endpoint

All primary endpoints will be analyzed in a descriptive way. Exact 95% CIs will be calculated for the objective response rate using Blythe-Still-Casella method.

#### 5.5.5.2 Secondary Efficacy Endpoint

PFS is defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first. Data for subjects who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued the study, or have initiated non-protocol anti-tumor therapy (NPT) will be censored on last assessment (or, if no post-baseline tumor assessment, at the time of first dose plus 1 day). Duration of PFS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of PFS will be computed using the formula proposed by Brookmeyer and Crowley.

OS is defined as the time from first dose to death from any cause. Data for subjects who are still alive at the time of data cutoff date, lost to follow-up, have discontinued the study (or, if no post-baseline assessment, at the time of first dose plus 1 day) will be censored at the date last known to be alive. Duration of OS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of OS will be computed using the formula proposed by Brookmeyer and Crowley.

For GRFS events are defined as grade 3-4 acute GVHD, chronic GVHD requiring systemic therapy, relapse, or death from any other reason. Duration of GRFS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of GRFS will be computed using the formula proposed by Brookmeyer and Crowley.

The RI and NRM will be calculated using cumulative incidence (CI) curves in a competing risks setting, death in remission being treated as a competing event to relapse. To estimate CI of acute or chronic GVHD, relapse and death will be considered competing events.

### 5.5.6 Biomarker Analyses

Additional PD, PK, and biomarker analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques.

## 6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording, AEs, and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

### 6.1 DEFINITIONS

### 6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL, MCL or GvHD that were not present before the AE reporting period (see Section 4.3).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms

cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

### 6.1.2 Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

### 6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death]

## 6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF.

### 6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the 30 days of the last acalabrutinib dose. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. If any SAE occurs beyond 30 days after the last dose of acalabrutinib ***AND*** it is assessed by the investigator as related to acalabrutinib, it must be reported as an SAE.

### 6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject,

discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be reported as AEs if they cannot be determined as exclusively due to progression.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 4 for more detail on assessing relationship.

### 6.2.3 Pregnancy

Investigators should report all pregnancies and pregnancies in the partners of subjects to the Sponsor within 24 hours. The Sponsor should report all occurrences to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma per contractual guidelines.

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days [2-day guidance applicable to acalabrutinib monotherapy only] after the last dose of study medication or 6 months after the alloSCT will be reported, followed to conclusion, and the outcome reported.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug [guidance applicable to acalabrutinib monotherapy only]. The

investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

### 6.2.4 Expedited Reporting Requirements for Serious Adverse Events

Investigators should report all SAEs to the Sponsor within 24 hours using the SAE Reporting Form. The Sponsor should report all SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma per contractual guidelines.

Whenever possible, SAEs should be reported by diagnosis term not as a constellation of symptoms. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

### 6.2.5 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

## 7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

The Sponsor retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis

- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

### 7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, current Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

This clinical study was designed and will be implemented in accordance with the protocol, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations (CFR) Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

### 7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

The investigator, or designee, must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with regulatory agencies and IRBs/IECs. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's

responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

### 7.3 SUBJECT SCREENING LOG

The investigator will keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

### 7.4 CASE REPORT FORMS

Authorized study site personnel will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly.

### 7.5 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules must be kept in a limited access cabinet or space. The study drug must not be used outside the context of the protocol.

### 7.6 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information, subject files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

The investigator shall retain study records in accordance with institutional and/or national/local regulations, whichever is longer.

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## APPENDICES

## Appendix 1. Schedule of Assessments

| | Screening | Treatment period | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before alloSCT | | | | | | At alloSCT | After alloSCT |
| Study month | -1 - 0 | 1 | 2 | 3 | 4 | 5 | 6 | | 1,3,6,9,12,15,18 |
| Physical examination | x | x | x | x | x | x | x | x | x |
| Medical history, including AE, SAE data collection | x | x | x | x | x | x | x | x | x |
| Rai staging | x | | | | | | | | |
| ECOG performance status | x | x | x | x | x | x | x | x | x |
| Vital signs (pulse, BP, temp.) | x | x | x | x | x | x | x | x | x |
| ECG | x | | | | | | | | |
| Urine or serum pregnancy test | x | | | | | | | x | 12 months after allo-SCT |
| FBC | x | x | x | x | x | x | x | x | x |
| U&E and LFT[1] | x | x | x | x | x | x | x | x | x |
| HBV, HCV, HIV serology[2] | x | | | | | | | | |
| Serum immunoglobulins (IgG, IgM, IgA) | x | | | x | | | x | x | x |
| $ß_2$-microglobulin | x | | | | | | | | |
| Coombs test | x | | | | | | | | |
| Urine analysis | x | | | | | | | | |
| FISH panel, p53 mutation status* | x | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| IgVH mutation status* | x | | | | | | | | |
| Tumor evaluation (imaging studies) | x | | | x | | | x | x | see 3.1.1 for details |
| MRD assessment by flow cytometry* | x | | | x | | | x | x | x |
| Chimerism | | | | | | | | | Until full donor chimerism |
| Immune parameters evaluation by flow cytometry* | x | | | x | | | x | x | x |
| Blood samples for additional assessments | x | | | x | | | x | x | x |

(*) – procedures performed by the central lab.

(1) – U&E and LFT include: calcium, chloride magnesium, phosphate/phosphorus, potassium, sodium ALT, AST, total bilirubin albumin, alkaline phosphatase, , bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, lactate dehydrogenase (LDH),total protein, and uric acid.

(2) – hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody

## Appendix 2. Performance Status Scores

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, 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 |

As published in Am J Clin Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

## Appendix 3. Known Strong in Vivo Inhibitors or Inducers of CYP3A

| Strong Inhibitors of CYP3A[a] | Strong Inducers of CYP3A[d] |
|---|---|
| boceprevir | carbamazepine[e] |
| clarithromycin[b] | phenytoin[e] |
| conivaptin[b] | rifampin[e] |
| indinavir | St John's wort[e] |
| itraconazole[b] | |
| ketoconazole[b] | |
| lopinavir/ritonavir[b] (combination drug) | |
| mibefradil[c] | |
| nefazodone | |
| nelfinavir | |
| posaconazole | |
| ritonavir[b] | |
| saquinavir | |
| telaprevir | |
| telithromycin | |
| voriconazole | |

a. A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
e. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Sponsor of the protocol.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 11 June 2015: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

## Appendix 4. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?
No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

## Appendix 5 IWCLL Response evaluation (according to Hallek)

### Definition of response, relapse and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and bone marrow. The timing of response assessment for therapies with a defined treatment duration (such as chemoimmunotherapeutic approaches) should be at least 2 months after completion of therapy. To define the response to therapy, two groups of parameters need to be assessed and documented: parameters of group A assess the lymphoid tumor load and constitutional symptoms, while parameters of group B assess the hematopoietic system (Table).

For continued therapies or treatment strategies that contain a maintenance phase, the assessment of response should be performed at least 2 months after patients achieve their maximum response or at a time point that is predefined in the protocol; in this case, it is not necessary to interrupt therapy for response assessment. Maximum response can be defined as a treatment phase where no additional improvement is seen during at least 2 months of therapy. In clinical trials, any response (e.g. CR, PR) should be sustained for at least 2 months prior to using this response in the assessment. In addition, where appropriate, a further assessment of response (i.e. marrow assessment) may be performed at least 2 months after the patient has cleared minimal residual disease from the peripheral blood.

1. Complete remission (CR) requires all of the following criteria (Table 4):

1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4.000/µl ($4x10^9$/L).

1.2. Absence of significant lymphadenopathy by physical examination. In clinical trials, a CT scan of the neck, abdomen, pelvis and thorax is desirable if previously abnormal. Lymph nodes should be < 1,5 cm in longest diameter. Once this is determined, further imaging should not be required until disease progression is apparent by clinical examination or on blood testing.

1.3. No splenomegaly or hepatomegaly by physical examination. In clinical trials, a CT

scan of the abdomen should be performed at response assessment and should show no evidence for lymphadenopathy and splenomegaly. We propose to use a recent consensus response cutoff for splenomegaly of 13 cm in cranio-caudal length.[96,97] However, the persistence of splenomegaly may not correlate with outcome.[96] The quantitative determination of hepatomegaly seems more difficult; changes such as focal or disseminated hepatic nodules support liver involvement.

1.4. Absence of disease-related constitutional symptoms. 5.1.5. Blood counts above the following values:

1.5.1. Neutrophils ≥1.500/µL. 5.1.5.2. Platelets ≥100.000/µL. 5.1.5.3. Hemoglobin ≥ 11,0 g/dL (without red blood cell transfusions).

1.6. Minimal residual disease assessment.

In clinical trials aimed at maximizing the depth of remission, the presence of minimal residual disease (MRD) after therapy should be assessed (see section 5.9.). The sensitivity of the method used to evaluate for MRD should be reported, as should be the tissue studied (blood or marrow). The proportion of patients achieving undetectable MRD should be reported with the total number of patients treated with the specific therapy as the denominator (not as a proportion of responders or those in complete remission).

1.7. For patients in clinical trials (Table 3): a bone marrow aspirate and biopsy should be performed if clinical and laboratory results listed in 5.1.1 to 5.1.5 demonstrate that a CR may have been achieved. To define a CR, the cytological or pathological evaluation of the bone marrow smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria. This evaluation is not based on a flow cytometry- based MRD assessment (see section 9).

In a clinical trial, the time point of marrow biopsy should be defined by the protocol. For example, in patients receiving chemo(immuno)therapy, the time point of marrow biopsy is typically 2 months post therapy.

When performing marrow biopsies in clinical trials, lymphoid nodules can be found that may reflect residual disease.[98,99] These nodules may be recorded as “nodular PR”.

Immunohistochemistry may be performed to define whether the nodules are comprised primarily of T cells, of B cells other than CLL cells or of CLL cells. If nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks or later, when peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. In cases, where a marrow biopsy was obtained at baseline, a comparison of pre- versus post-therapy biopsies should be performed. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.

In clinical trials aimed at maximizing the response rate, the quality of the response should be assessed in the marrow for MRD by highly sensitive molecular based assays or immunophenotyping (see section 5.9.).

1.8. Some patients fulfill all the criteria for a CR (including the marrow examinations described in 5.16), but have a persistent anemia, thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (see 5.1.7) should be performed with scrutiny and not show any clonal disease infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with non-cytopenic CR.

2. To define a partial remission (PR), at least one parameter of group A and one parameter of group B need to improve, if previously abnormal (see Table 4 and sections 5.2.1-5). If only one parameter of both groups A and B was abnormal prior to therapy, only 1 needs to improve. Constitutional symptoms persisting for more than 1 month should be recorded.

2.1. A decrease in the number of blood lymphocytes to 50% or less from the value prior to therapy.

2.2. Reduction in lymphadenopathy compared to baseline (by cross-sectional imaging scans in clinical trials or by palpation in general practice) as defined by:

2.2.1 A decrease in lymph node size by 50% or more in

- the sum of the products of the same enlarged lymph nodes selected at baseline as assessed by imaging (an established number in clinical trials of lymph nodes has been up to 6).
- and the sum of longest diameters of the same enlarged lymph nodes selected at baseline as assessed by physical exam (an established number in clinical trials of lymph nodes has been a maximum of 6).

2.2.2 No increase in any lymph node, and no new enlarged lymph node (diameter ≥1,5 cm). For small lymph nodes (longest diameter < 1,5 cm), an increase of < 25% is not considered to be significant.

2.3. A regression of ≥50% of the extent of enlargement of the spleen below the costal margin defined by palpation, or normalization in size. When assessed by CT, scan spleen size must have regressed by ≥50% in length beyond normal.[96] A persistence of splenomegaly post therapy may have limited influence on outcome in CLL.[96]

2.4. A regression of ≥50% of the extent of enlargement of the liver below the costal margin defined by palpation, or normalization in size. Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

2.5. The blood count should show one of the following results:

2.4.1. Platelet counts greater than 100.000/µL or 50% improvement over baseline.

2.4.2. Hemoglobin greater than 11,0 g/dL or 50% improvement over baseline without red blood cell transfusions or erythropoietin support.

3. Progressive disease (PD) during or after therapy is characterized by at least one of the following, when compared to nadir values (Table 4):

3.1. Lymphadenopathy: Progression of lymphadenopathy is often discovered by physical examination and should be recorded at regular intervals. In CLL, the use of imaging (CT scans) usually does not add much information for the detection of progression or relapse.[100] Disease progression occurs, if one of the following events below is

observed:

- Appearance of any new lesion such as enlarged lymph nodes ( ≥1,5 cm), splenomegaly, hepatomegaly or other organ infiltrates. Transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as PD.

- An increase by 50% or more in greatest determined diameter of any previous site ( ≥ 1,5 cm).

3.2. An increase in the spleen size by 50% or more or the de novo appearance of splenomegaly. In the setting of splenomegaly, the splenic length must increase by ≥50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to ≥16 cm). If no prior splenomegaly was observed at baseline or if splenomegaly has resolved with treatment, the spleen must increase by at least 2 cm from baseline.

3.3. An increase in the liver size of ≥50% of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly. Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

3.4. An increase in the number of blood lymphocytes by 50% or more with at least 5.000 B- lymphocytes per µL. Certain therapies (for example kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count, by itself, does not uniformly indicate an increased tumor burden, but may reflect re- distribution of leukemia cells from lymphoid tissues to the blood. This should be pre-defined in the protocol of clinical trials for therapies where re-distribution of disease occurs. In such cases, increased lymphocytosis alone is not a sign of treatment failure or progressive disease.

.3.5. Transformation to a more aggressive histology (Richter syndrome or Richter transformation). The diagnosis of Richter transformation should be established by lymph node or other tissue biopsy.

3.6. Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) directly

attributable to CLL and unrelated to autoimmune cytopenias.

3.6.1 During therapy: cytopenias may occur as a side effect of many therapies and should be assessed according to Table 5. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

3.6.2. Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by $\geq$2 g/dl or to < 10 g/dl, or by a decrease of platelet counts by $\geq$50% or to < 100.000/µl, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy is consistent with the cytopenia due to increased marrow infiltration of clonal CLL cells and is not considered a treatment related toxicity.

4. Stable disease: Patients who have not achieved a CR or a PR, and who have not exhibited PD, will be considered to have stable disease (which is equivalent to a non-response).

5. Treatment failure: Responses that should be considered clinically beneficial include CR and PR; all others (e.g. stable disease, non-response, progressive disease, or death from any cause) should be rated as a treatment failure.

6. Time to next treatment, progression-free survival, event-free survival, and overall survival.

“Progression-free survival” (PFS) is defined as the interval between the first treatment day (in phase III trials: day of randomization for intent-to-treat analysis) to the first sign of disease progression or death from any cause.

“Event-free survival” (EFS) is defined as the interval between the first treatment day (in phase III trials: day of randomization for intent-to-treat analysis) to the first sign of disease progression or start of a new treatment or withdrawal from the trial due to toxicity or death (whichever occurs first).

“Overall survival” (OS) is defined as the interval between the first treatment day (in phase III trials: day of randomization for intent- to-treat analysis) to death. “Time to next treatment” is defined as interval between the first treatment day until the patient starts an

alternative therapy for progressive CLL.

Please note that the response duration may be assessed during therapy for continuous treatment, in particular with oral agents, as well as after the end of treatment, in particular with chemo(immuno)therapy. Study protocols should provide detailed specifications of the planned time points for the assessment of the treatment response under continuous therapy. Response durations of less than six months are not considered clinically relevant (see refractory disease, 8.).

7. Relapse

Relapse is defined as evidence of disease progression (see 3) in a patient who has previously achieved the above criteria of a CR or PR (5.1-5.2) for a period of 6 or more months.

8. Refractory disease

Refractory disease is defined as treatment failure (as defined in 5.5) or as progression within 6 months from the last dose of therapy.

9. Minimal residual disease

The complete eradication of the leukemia is a desired endpoint. Use of sensitive multicolor flow cytometry, PCR, or next-generation sequencing can detect minimal residual disease (MRD) in many patients who achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become well standardized. Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of less than one CLL cell in 10.000 leukocytes.[108] Refinement and harmonization of these technologies has established that a typical flow cytometry-based assay comprises a core panel of six markers (i.e. CD19, CD20, CD5, CD43, CD79b and CD81). As such, patients will be defined as having undetectable MRD (MRD- neg) remission if they have blood or marrow with less than one CLL cell per 10.000 leukocytes. The blood generally can be used for making this assessment, as the marrow will have detectable CLL when it is also found in the peripheral blood. However, there

are therapies that preferentially clear the blood but not the marrow (such as monoclonal antibodies). Therefore, it may be important to confirm that the marrow aspirate also is MRD-neg when the blood is found to be MRD-neg. Clinical trials aimed at maximizing the depth of remissions should include at least one test to assess for MRD, because the lack of leukemia persistence using these sensitive tests has a strong, positive prognostic impact. The report should be clear as to whether blood and/or marrow have been assessed and should report the proportion of MRD-neg patients on an intent-to-treat basis using the total number of patients in that treatment arm as the denominator (not those assessed or those who responded to treatment).

**Table Appendix 5 - Response definition after treatment for CLL patients**

| Group | PARA-METER | CR | PR | PD | SD |
|---|---|---|---|---|---|
| A | Lymph nodes | None ≥1,5 cm | Decrease 50% (from baseline) 1) ≥ | Increase 50% from baseline or from response > | Change of -49% to +49% |
| | Liver and/or spleen size* | Spleen size < 13 cm; liver size normal | Decrease 50% (from baseline) ≥ | Increase 50% from baseline or from response > | Change of -49% to +49% |
| | Constitutional symptoms | None | Any | Any | Any |
| | Circulating lymphocyte count | Normal | Decrease 50% from baseline > | Increase 50% over baseline > | Change of -49% to +49% |
| B | Platelet count | 100.000/µl ≥ | 100.000/µl or increase 50% over baseline ≥ ≥ | Decrease of 50% from baseline secondary to CLL > | Change of -49 to +49% |
| | Hemoglobin | 11,0 g/dl (untransfused and without erythropoietin) | 11 g/dl or increase 50% over baseline ≥ ≥ | Decrease of ≥2 g/dl from baseline secondary to | Increase < 11,0 g/dl or < 50% over baseline, or decrease < |

| | | | | | |
|---|---|---|---|---|---|
| | | ≥ | | CLL | 2 g/dl |
| | Marrow | Normocellular, no CLL cells, no B-lymphoid nodules. | Presence of CLL cells, or of B-lymphoid nodules, or not done | Increase of CLL cells by ≥50% on successive biopsies | No change in marrow infiltrate |

1) Sum of the products of 6 or less lymph nodes (as evaluated by CT scans and physical exam in clinical trials, or by physical exam in general practice).

Table 6. Response Definitions for Clinical Trials [31]

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

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