7.2 Phase II

The phase II part of the trial is an open-label, 1:1 randomized, multicenter prospective study with 4 interim analyses for safety and efficacy of the combination treatment.

Details of all treatments (dose and schedule) are given in paragraph 9. No formal comparison will be made between the 2 arms.

8 Study population

8.1 Population (base)

In this trial, 6-18 CLL patients will be treated in the phase I part and an additional 84 CLL patients will be recruited in the phase II part (6 patients from the phase I part treated at the RP2D will be counted also in the population of the phase II part). Additionally, a maximum of 10 SLL patients will be included during the phase II part. Patients with relapsed or refractory CLL/SLL (patients with SLL can only be included in the phase II part), after at least one prior line of treatment (any approved regimen; may include treatment with a BTKi and/or venetoclax) may be included (see chapter 14.1 for sample size calculation).

8.2 Eligibility for registration and randomization

All patients must be registered before start of treatment and must meet all of the following eligibility criteria.

8.2.1 Inclusion criteria

- Documented relapsed or refractory CLL or SLL (SLL in phase II part only) following at least one systemic 1st-line treatment
- Requiring treatment according to IWCLL criteria (**appendix A**);
- Age at least 18 years;
- ECOG/WHO performance status 0-2;
- In case of prior venetoclax treatment, enrollment can only occur at least 24 months after end of treatment and patients must not have progressed during venetoclax treatment;
- Adequate BM function defined as:
  - Hemoglobin >5.6 mmol/l or Hb > 9 g/dL, unless low Hb is directly attributable to CLL/SLL infiltration of the BM, proven by BM biopsy;

- Absolute neutrophil count (ANC) >1.0 x 10^9/L (1,000/µL), unless low ANC is directly attributable to CLL/SLL infiltration of the BM, proven by BM biopsy;
- Platelet count >30 x 10^9/L (30,000/µL), unless low platelets is directly attributable to CLL/SLL infiltration in the BM;

- Estimated Glomerular Filtration Rate (eGFR) (MDRD) or estimated creatinine clearance (CrCl) ≥ 50ml/min (Cockcroft-Gault **appendix 0**);
- Adequate liver function as indicated:
  - Serum aspartate transaminase (ASAT) and alanine transaminase (ALAT) ≤ 3.0 x upper limit of normal (ULN);
  - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or controlled autoimmune hemolytic anemia);
- Prothrombin time (PT)/International normal ratio (INR) <1.5x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN; unless receiving anticoagulation;
- Negative serological testing for hepatitis B virus (HBV) (Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) negative) and hepatitis C virus (hepatitis C antibody). Patients who are positive for anti-HBc or hepatitis C antibody may be included if they have a negative PCR within 6 weeks before enrollment. Those who are PCR positive will be excluded;
  Please note: For patients positive for anti-HBc or antibodies for hepatitis C, HBV-DNA or HCV-DNA PCR, respectively, has to be repeated every month until 12 months after last dose of study treatment;
- Patient is able and willing to adhere to the study visit schedule and other protocol requirements;
- Patient is capable of giving informed consent;
- Written informed consent.

8.2.2 Exclusion criteria

- Active CLL/SLL directed therapy within the last 14 days;
- Prior treatment with a CD3 × CD20 bispecific antibody or CAR T-cell therapy
- Transformation of CLL (Richter's transformation);
- Prior allogeneic stem cell transplantation and/or solid organ transplantation;
- Patient with a history of confirmed progressive multifocal leukoencephalopathy (PML);
- Malignancies other than CLL/SLL currently requiring systemic therapy or not treated in curative intention or showing signs of progression after curative treatment;
- Known allergy to xanthine oxidase inhibitors and/or rasburicase;

- History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components);
- Active bleeding or uncontrolled severe bleeding diathesis (*e.g.,* hemophilia or severe von Willebrand disease);
- Active fungal, bacterial, and/or viral infection CTCAE grade > 1;
  Please note: active controlled as well as chronic/recurrent infections are at risk of reactivation/infection during treatment;
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled: infection, auto-immune hemolysis, immune thrombocytopenia, diabetes, hypertension, hyperthyroidism or hypothyroidism etc.);
- Patient known to be HIV-positive;
- Patient requiring treatment with a strong cytochrome P450 (CYP) 3A inhibitor/inducer (see **appendix I**);
- CTCAE grade III-IV cardiovascular disease including but not limited to:
  - Unstable or uncontrolled disease/condition related to or affecting cardiac function, eg, unstable angina, congestive heart failure grade III or IV as classified by the New York Heart Association (see **appendix A**), uncontrolled clinically significant cardiac arrhythmia (CTCAE grade II or higher), or clinically significant electrocardiogram (ECG) abnormalities.
  - Myocardial infarction within 6 months prior to registration.
  - Subject age ≥75 and 2 or more active grade ≥2 cardiovascular conditions.
  - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec. NOTE: this criterion does not apply to subjects with a left bundle branch block.
  - Stroke or intracranial hemorrhage within 6 months prior to registration.
- Severe pulmonary dysfunction (CTCAE grade III-IV, see **appendix D**);
- Severe neurological or psychiatric disease (CTCAE grade III-IV, see **appendix D**);
- Neuropathy > CTCAE grade II
- Patient who has difficulty with or are unable to swallow oral medication, or have significant gastrointestinal disease that would limit absorption of oral medication;
- Vaccination with live vaccines within 28 days prior to registration;
- Use of any other experimental drug or therapy within 28 days of registration;
- Major surgery within 28 days prior to registration;
- Pregnant women and nursing mothers;
- Fertile men or women of childbearing potential (WOCBP) unless: (1) surgically sterile or ≥ 2 years after the onset of menopause; (2) willing to use a highly effective contraceptive method

such as oral contraceptives, intrauterine device or sexual abstinence during study treatment and for 12 months after last dose of epcoritamab and 30 days after last dose of venetoclax;

- Previous participation in the HO139 CLL or HO140 CLL trial and eligible for and willing to participate in the HO159 CLL trial;
- Current participation in other clinical trial with medicinal products;
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

9 Treatment

9.1 Treatment schedule

9.1.1 Venetoclax ramp up

Both during the phase I and the phase II part of the trial, for both arms of the trial, all patients should start with ramp-up of venetoclax (see treatment schedule below) within 28 days after registration. Assessment of patient-specific factors for level of risk of TLS and providing prophylactic hydration and anti-hyperuricemics to patients prior to first dose of venetoclax to reduce risk of TLS is mandatory (see **appendix H**). Venetoclax will be administered orally once daily. The initial venetoclax dose is 20 mg. After one week of treatment at 20 mg, the dose will be escalated to 50 mg, followed by subsequent increases, each after one week, to 100 mg, 200 mg and the maximum dose of 400 mg. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS and CRS.

Arm A and B: Venetoclax ramp-up prior to start of epcoritamab

Agent	Dose/day	Route of administration	Cycle	Days
Venetoclax	20 mg	Oral	ramp-up	1-7
Venetoclax	50 mg	Oral	ramp-up	8-14
Venetoclax	100 mg	Oral	ramp-up	15-21
Venetoclax	200 mg	Oral	ramp-up	22-28
Venetoclax	400 mg	Oral	ramp-up	29-35

9.1.2 Venetoclax and epcoritamab combination treatment

The treatment schedule is the same for phase I and phase II patients. After venetoclax ramp-up, all patients will receive 26 cycles of venetoclax. Each cycle has a duration of 28 days. All patients will commence treatment with epcoritamab after completion of the venetoclax ramp-up phase. Epcoritamab will be subcutaneously administered from cycle 1, starting with a priming (0.16 mg) and intermediate (0.8 mg) dose before administering the first full dose. Patients will be treated with