4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Treatment-naïve (TN) adult patient ≥ 18 years with confirmed diagnosis of CLL that meets the iwCLL criteria (Hallek et al 2018).
2. For those patients with a screening lymphocyte count < 5000 cells/µL, historical data confirming a lymphocyte count ≥ 5000 cells/µL at time of CLL diagnosis is required.
3. CLL requiring treatment as defined by ≥ 1 of the following criteria:
   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Hemoglobin concentrations < 10 g/dL or platelet counts < 100 x 10^9 cells/L are generally regarded as indications for treatment.
   b. Massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly.
   c. Massive (ie, ≥ 10 cm in longest diameter [LDi]), progressive or symptomatic lymphadenopathy.
   d. Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period, or lymphocyte doubling time (LDT) < 6 months.
   NOTE: LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts < 30 x 10^9 cells/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (eg, infections and steroid administration) should be excluded.
   e. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, and spine).
   f. Disease-related symptoms as defined by any of the following:
      – Unintentional weight loss ≥ 10% within the previous 6 months.
      – Fevers ≥ 100.5°F or ≥ 38.0°C for 2 or more weeks without evidence of infection.
      – Night sweats for ≥ 1 month without evidence of infection.
      – Significant fatigue (ie, ECOG [Eastern Cooperative Oncology Group] performance score of 2 or worse; cannot work or unable to perform usual activities).

        NOTE: Patients with significant fatigue cannot have an ECOG score of 0.
4. ECOG score 0, 1, or 2.
5. Measurable disease by CT/MRI. Measurable disease is defined as ≥ 1 lymph node > 1.5 cm in LDi and measurable in 2 perpendicular diameters.

6. Adequate marrow function as defined by:
   a. Absolute neutrophil count ≥ 1.0 x 10^9 cells/L with an exception for patients with bone marrow involvement, in which case absolute neutrophil count must be ≥ 0.75 x 10^9 cells/L (without growth factor support within past 14 days).
   b. Platelet counts ≥ 75 x 10^9 cells/L; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator), platelet count should be ≥ 50 x 10^9 cells/L (without growth factor support or transfusion within past 14 days).
   c. Hemoglobin > 75 g/L (may be post-transfusion).
7. Adequate liver function as indicated by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x the institutional upper limits of normal (ULNs) value; serum total bilirubin < 3.0 x ULN (unless documented Gilbert's syndrome).
8. Adequate renal function as defined as creatinine clearance ≥ 50 mL/min directly measured with a 24-hour urine collection or calculated according to the modified formula of Cockcroft-Gault equation or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation (see Appendix 22).
9. Life expectancy > 6 months.
10. Signed informed consent and able to comply with the study protocol in the investigator's judgment.
11. Women of childbearing potential must be willing to use a highly effective method of birth control (Note: when oral hormonal contraceptives are selected, an additional barrier method is required; see Appendix 23) for the duration of the study and for:
    - ≥ 90 days after the last dose of SZ, or
    - ≥ 18 months after the last dose of VO

    (Note: Investigational medicines may cause nausea, vomiting and diarrhea; oral hormonal contraceptives cannot be considered highly effective in this setting.)

    They must also have a negative serum pregnancy test result ≤ 7 days before randomization.
12. Nonsterile men must be willing to use a highly effective method of birth control and must refrain from donating sperm for the duration of the study and for:
    - ≥ 90 days after the last dose of SZ, or
    - ≥ 18 months after the last dose of VO

    A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.

    Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Previous systemic treatment for CLL. Note: Up to 4 doses of anti-CD-20 antibody specifically for autoimmune cytopenia is allowed; the last dose should be given ≥ 6 months before screening).
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation (biopsy based on clinical suspicion may be needed to rule out transformation).
3. Known central nervous system involvement.
4. Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML).
5. Severe or debilitating pulmonary disease, defined as chronic supplementation of oxygen and/or respiratory failure requiring assisted ventilation.
6. Clinically significant cardiovascular disease including the following:
   a. Myocardial infarction within 6 months before screening.
   b. Unstable angina within 3 months before screening.
   c. New York Heart Association class III or IV congestive heart failure (see Appendix 4).
   d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes).
   e. QTcF > 480 msecs based on Fridericia's formula.
      – NOTE: QTcF value may be calculated as the numerical average of up to 3 separate readings for eligibility.
   f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place.
   g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening.
7. Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia requiring treatment.
8. History of prior malignancy, except for conditions as listed below and as long as patients have recovered from the acute side effects incurred because of previous therapy:
   a. Malignancies surgically treated with curative intent and with no known active disease present for ≥ 3 years before randomization.
   b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease.
   c. Adequately treated cervical carcinoma in situ without evidence of disease.
   d. Localized prostate cancer with Gleason score ≤ 6.
9. Use of investigational agents within the last 4 weeks before screening.
10. Active fungal, bacterial, and/or viral infection requiring systemic therapy.

11. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products.
12. Hypersensitivity to zanubrutinib, sonrotoclax, obinutuzumab, venetoclax, or any of its excipients (eg, trehalose).
13. Pregnant women and nursing mothers.
14. Vaccination with a live vaccine for a minimum of 28 days before enrollment (see also prohibited medications, Section 6.2.2).
15. Prisoners or patients who are institutionalized by regulatory or court order or persons who are in dependence to the sponsor or an investigator.
16. History of illicit drug use or alcohol abuse within 12 months before randomization in the investigator's judgment.
17. Positive HIV serology (HIVAb) status or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg).
    b. Patients with presence of hepatitis B core antibody (HBcAb), in the absence of HBsAg, with detectable hepatitis B virus (HBV) DNA.
        – NOTE: the limit of detection for HBV DNA must have a sensitivity of < 20 IU/mL; see Section 7.4.4.5) Patients with presence of HBcAb but undetectable HBV DNA and if they are willing to undergo HBV DNA monitoring every 4 weeks for HBV reactivation are eligible.
    c. Patients with presence of hepatitis C virus (HCV) antibody and HCV RNA detectable (NOTE: the limit of detection for HCV RNA must have a sensitivity of < 15 IU/mL; see Section 7.4.4.5. Patients with presence of HCVAB and undetectable HCV RNA and if willing to undergo HCV RNA monitoring every 4 weeks for HCV reactivation are eligible).
18. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in the study.
19. Requires the use of warfarin, marcumar, phenprocoumon (because of potential drug-drug interactions with venetoclax that may potentially increase the exposure of warfarin or phenprocoumon), or vitamin K antagonist.
20. Receiving treatment with any moderate or strong CYP3A4 inhibitor (Appendix 5) (≤ 7 days or 5 half-lives) or strong CYP3A4 inducer (≤ 14 days or 5 half-lives) before the first dose of study drug, or requiring ongoing treatment with a moderate or strong CYP3A inhibitor or a strong CYP3A inducer.
21. Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days before the first dose of study drug.
22. Unable to swallow capsules or tablets or diseases significantly affecting GI function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery

procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

23. At time of enrollment, receiving systemic corticosteroids unless administered for adrenal replacement.