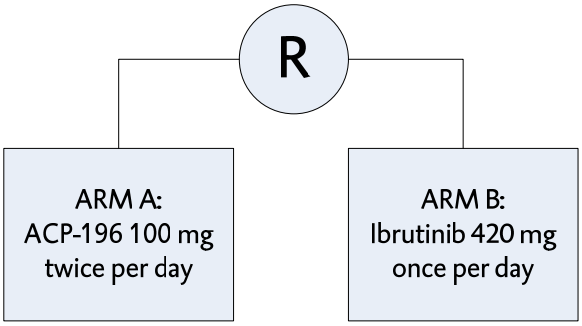
SAMENVATTING ACE-CL-006

TITEL

A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia

STUDIESCHEMA



INCLUSIECRITERIA

- Men and women ≥ 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- Diagnosis of CLL that meets published diagnostic criteria(Hallek 2008):
    - o Monoclonal B-cells (either kappa or lambda lightchain restricted) that are clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, or CD23) and CD5.
    - o Prolymphocytes may comprise ≤ 55% of blood lymphocytes.
    - o No evidence of cyclin D1 rearrangement or BCL-1 over expression.
- Must have ≥ 1 of the following high-risk prognostic factors:
    - o Presence of 17p del by central laboratory
    - o Presence of 11q del by central laboratory
- Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment:
    - o Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/μL).
    - o Massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
    - o Massive nodes (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy.
    - o Progressive lymphocytosis with an increase of > 50% over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months.
    - o Autoimmune anemia and/or thrombocytopenia thatis poorly responsive to standard therapy.
    - o Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs:
        - Unintentional weight loss ≥ 10% within the previous 6 months before Screening.
        - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks before Screening without evidence of infection.
        - Night sweats for > 1 month before Screening without evidence of infection.
- Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as ≥ 1 lymph node > 1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended.
- Must have received ≥ 1 prior therapies for CLL.
- Meet the following laboratory parameters:

- o Absolute neutrophil count (ANC) ≥ 750 cells/µL (0.75 x 10^9/L) or ≥ 500 cells/µL (0.50 x 10^9/L) in subjects with documented bone marrow involvement and independent of growth factor support 7 days before assessment.
- o Platelet count ≥ 30,000 cells/µL (30 x 10^9/L) without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded.
- o Serum aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) < 3.0 x upper limit of normal (ULN).
- o Total bilirubin ≤ 2.5 x ULN.
- o Estimated creatinine clearance (ie, estimated glomerular filtration rate [eGFR] using Cockcroft-Gault) ≥ 30 mL/min.

• Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations at the institution that administers study drug for the entire study.
• Women of childbearing potential who are sexually active with a male partner must have a negative serum pregnancy test and agree to simultaneously use 2 forms of acceptable methods of contraception (eg, condom and with either implants, injectable, oral, or intrauterine forms of contraceptives) while on the study and for 30 days after the last dose of ACP-196 or ibrutinib. Postmenopausal women (> 45 years of age and without menses for > 1 year) and surgically sterilized women are exempt from this criterion.
• Men must agree to use acceptable methods of contraception during the study and for 30 days after the last dose of ACP-196 or ibrutinib if sexually active with a woman of childbearing potential.
• Men must agree to refrain from sperm donation during the study and for 30 days after the last dose of ACP-196 or ibrutinib.
• Are willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information.

EXCLUSION CRITERIA

• Known central nervous system (CNS) lymphoma or leukemia.
• Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
• Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone daily or equivalent).
• Prior exposure to ibrutinib or to a B-cell receptor (BCR) inhibitor (eg, Bruton tyrosine kinase [Btk] inhibitors or phosphoinositide-3 [PI3] kinase inhibitors or Syk inhibitors) or a BCL-2 inhibitor (eg, ABT-199).
• Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
• Corticosteroid use > 20 mg within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. Subjects requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.
• Prior radio- or toxin-conjugated antibody therapy.
• Prior allogeneic stem cell transplant or autologous transplant.
• Major surgery within 4 weeks before first dose of study drug.
• History of prior malignancy except for the following:
  - o Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years before Screening and felt to be at low risk for recurrence by treating physician
  - o Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer
  - o Adequately treated cervical carcinoma in situ without current evidence of disease

• Currently active clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or history of myocardial infarction within 6 months before first dose with study drug.
• Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
• Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment.
• Known history of infection with human immunodeficiency virus (HIV).
• Serologic status reflecting active hepatitis B or C infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
• History of stroke or intracranial hemorrhage within 6 months before randomization.
• History of bleeding diathesis (eg, hemophilia, von Willebrand disease). Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug.
• Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
• Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
• Breast feeding or pregnant.
• Concurrent participation in another therapeutic clinical trial.