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

Published: 25-06-2015
Last updated: 19-04-2024

Therapy:The investigational product, ACP-196, will be supplied as hardgelatin capsules for oral administration.Commercially available ibrutinib (IMBRUVICA®) will be used asthe reference therapy.Objectives: Primary Objective:To assess whether ACP-196...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54575

Source
ToetsingOnline

Brief title
ACE-CL-006

Condition

- Leukaemias

Synonym
blood cancer, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Acerta Pharma BV
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: ACP-196, Chronic Lymphocytic Leukemia, Ibrutinib, Open Label

Outcome measures

Primary outcome

To assess whether ACP-196 is non-inferior to ibrutinib with respect to

progression-free survival (PFS) based on independent review committee

(IRC) assessment in subjects with relapsed or refractory chronic

lymphocytic leukemia (CLL) with high-risk prognostic markers.

Secondary outcome

To compare between ACP-196 and ibrutinib in terms of:

• Incidence of Grade >= 3 infections

• Incidence of Richter*s transformation

• Incidence of atrial fibrillation

• OS

Study description

Background summary

This randomized controlled Phase 3 study is designed to assess whether ACP-196 is noninferior
to ibrutinib with respect to PFS in subjects with previously treated CLL who have highrisk
prognostic factors per NCCN guidelines (Version 2.2015). ACP-196 block some of the cell functions that cause CLL to grow and survive and may also help control the disease. Ibrutinib and ACP-196 are covalent inhibitors of Btk and thus

offer similar pharmacology as
the basis for comparative efficacy and safety. But ACP-196 seems to have less side effects.

See for more information protocol section 2 (rationale).

Study objective

Therapy:
The investigational product, ACP-196, will be supplied as hard gelatin capsules for oral administration.
Commercially available ibrutinib (IMBRUVICA®) will be used as the reference therapy.
Objectives: Primary Objective:
To assess whether ACP-196 is non-inferior to ibrutinib with respect to progression-free survival (PFS) based on independent review committee (IRC) assessment in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) with high-risk prognostic markers. The IRC will use the International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL, Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012)*hereafter referred to as IWCLL 2008 criteria.
Secondary Objectives:
To evaluate the benefit:risk of ACP-196 versus ibrutinib in terms of:
• Grade >= 3 infections
• Richter*s transformation
• Atrial fibrillation
• Overall survival (OS)

Study design

Approximately 500 eligible subjects will be randomized in a 1:1 ratio into 2 arms to receive either ACP-196 (Arm A; N=250) or ibrutinib (Arm B; N=250).
Randomization will be performed stratified by the following factors:
• Presence of 17p del
• ECOG performance status (ECOG = 2 versus ECOG <=1)
• Number of prior therapies (1-3 versus >= 4)
Subject participation will include a Screening Phase, a Treatment Phase, Post-treatment Phase and a Post-disease Progression Phase.
Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2008 criteria until

disease progression.

Intervention

ACP-196 100 mg Twice per Day (Treatment Arm A):
ACP-196 is provided as 100-mg hard gelatin capsules. ACP-196 100 mg will be orally administered twice per day (BID). Doses will be administered 12 hours apart with a window of ± 1 hour. ACP-196 will be administered daily until disease progression or unacceptable toxicity.
Ibrutinib 420 mg Once per Day (Treatment Arm B):
Commercially available ibrutinib supplied as hard gelatin capsules (140-mg strength) for oral administration will be administered per the IMBRUVICA approved label. Ibrutinib 420 mg (3 capsules) will be orally administered once per day (QD). Ibrutinib will be administered until disease progression or unacceptable toxicity

Study burden and risks

Patients will be asked to complete diaries and questionnaires. They should take IP every day as well.

Some side effects were observed in these clinical studies, which were considered related to ACP-196. Those that occurred in 10% or more of the patients, are listed below:
- Headache
- Bruising events (all mild/moderate only) including bruises, petechia, and increased tendency to bruise
- Diarrhea
- Fatigue /tiredness
- Nausea
- Cough (mild/moderate only)
- Upper respiratory tract infection (infection of the nose, throat or sinuses)
- Pain in joints or muscles, in the legs/feet, arms/hands or back
- Fever
- Constipation (bowel movements that are infrequent or hard to passmild/moderate only)
- Cough (mild/moderate only)
- Dizziness
- Vomiting
- Muscle pain
- Anemia
- Rash

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Men and women >= 18 years of age.
2. ECOG performance status of 0 to 2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008):
oMonoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing >= 1 B-cell marker (CD19, CD20, or CD23) and CD5.
oProlymphocytes may comprise <= 55% of blood lymphocytes.
oPresence of >= 5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis); this applies to CLL only.
4. Must have >= 1 of the following high-risk prognostic factors:
i. Presence of 17p del by central laboratory.
ii. Presence of 11q del by central laboratory.

5. Active disease meeting >= 1 of the following IWCLL 2008 criteria for requiring treatment:
a. 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).
b. Massive (ie, >= 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
c. Massive nodes (ie, >= 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy.
d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or a LDT of < 6 months. LDT may be obtained by linear regression extrapolation of ALC obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of < 30 X 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.
e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy.
f. 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:
i. Unintentional weight loss >= 10% within the previous 6 months before Screening.
ii. Significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities).
iii. Fevers > 100.5°F or 38.0°C for >= 2 weeks before Screening without evidence of infection.
iv. Night sweats for > 1 month before Screening without evidence of infection.
6. Must have received >= 1 prior therapies for CLL.
8. Meet the following laboratory parameters:
a. 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.
b. 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.
c. Serum AST/SGOT and ALT/SGPT <= 3.0 x ULN.
d. Total bilirubin <= 1.5 x ULN.
e. Estimated creatinine clearance (ie, eGFR using Cockcroft-Gault) >= 30 mL/min.
9. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations at the institution that administers study drug for the entire study.
10. Women who are sexually active and can bear children must agree to use highly effective
forms of contraception while on the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer.
11. Men who are sexually active and can beget children must agree to use highly

effective
forms of contraception during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer.
12. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer.
13. Must be 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 (in accordance with national and local subject privacy regulations). Note vulnerable subjects, as defined in the International Conference on Harmonisation (ICH) GCP, are not allowed on this protocol (eg, prisoners or institutionalized subjects).

Exclusion criteria

1. Known CNS lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter*s syndrome.
3. Uncontrolled AIHA or 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).
4. Prior exposure to ibrutinib or to a BCR inhibitor (eg Btk or PI3 kinase or Syk inhibitors) or a BCL-2 inhibitor (eg, ABT-199).
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
6. 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. For example, 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.
7. Prior radio- or toxin-conjugated antibody therapy.
8. Prior allogeneic stem cell or autologous transplant.
9. Major surgery within 4 weeks before first dose of study drug.
10. History of prior malignancy except for the following:
a. 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
b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer
c. Adequately treated cervical carcinoma in situ without current evidence of disease
11. 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 QTc > 480 msec at screening.
12. 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.
13. 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.
14. Known history of infection with HIV.
15. 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 PCR result before randomization. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
16. History of stroke or intracranial hemorrhage within 6 months before randomization.
17. History of bleeding diathesis (eg, hemophilia, von Willebrand disease).
18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
19. Requires treatment with a strong cytochrome CYP3A4 inhibitor/inducer.
20. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
21. Breastfeeding or pregnant.
22. Concurrent participation in another therapeutic clinical trial.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-09-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACP-196
Generic name:	acalabrutinib
Product type:	Medicine
Brand name:	Imbruvica
Generic name:	brutinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-06-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2023
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005530-64-NL
ClinicalTrials.gov	NCT02477696
CCMO	NL53353.018.15