An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia

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The purpose of this study is to evaluate the safety, pharmacokinetics, pharmacodynamics and activity of ACP-196 in treating subjects with Waldenström disease.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON53142

Source
ToetsingOnline

Brief title
ACE-WM-001

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Waldenström Macroglobulinemia; mobus Waldenström

Research involving
Human

Sponsors and support

Primary sponsor: ACERTA PHARMA, BV
Source(s) of monetary or material Support: Acerta Pharma BV

Intervention

Keyword: ACP-196, Waldenström Macroglobulinemia

Outcome measures

Primary outcome

To determine the ORR of acalabrutinib in subjects with WM as assessed by

investigators.

Secondary outcome

Secondary Objectives:

• To determine the ORR of acalabrutinib by IRC

• To determine the DOR of acalabrutinib by investigator and by IRC, respectively

• To determine the progression-free survival (PFS) of acalabrutinib by

investigator and by IRC, respectively

• To determine the overall survival (OS) of acalabrutinib

• To characterize the PK profile of acalabrutinib

• To characterize the safety of acalabrutinib

• To evaluate the effect of acalabrutinib in health-related quality of life

Exploratory Objective:

• To evaluate the PD effects of acalabrutinib

Study description

Background summary

Bruton tyrosine kinase (Btk) is an enzyme that is expressed among cells of hematopoietic origin, including B-cells. Btk regulates multiple cellular processes. Investigation from first generation Btk inhibitors in subjects with Waldenströms disease showed rapid reduction in IgM and improved hematocrit.

Acerta Pharma, has optimized novel Btk inhibitors and in nonclinical studies ACP-196 showed good results in activity and safety.

Study objective

The purpose of this study is to evaluate the safety, pharmacokinetics, pharmacodynamics and activity of ACP-196 in treating subjects with Waldenström disease.

Study design

This study is a multicenter (approximately 30 global centers) open-label clinical trial evaluating the safety and efficacy of acalabrutinib 100 mg twice a day (BID) in subjects with previously treated WM (N = 76) using a Simon's optimal two-stage design. In addition, a small cohort (N = 8 to 12) of subjects with previously untreated WM will be enrolled as an exploratory cohort to determine the preliminary safety and efficacy of acalabrutinib in this patient population. In the Netherlands (NL) and France, enrollment for the untreated WM cohort will begin after efficacy has been confirmed in Stage 1 of the Simon's optimal two-stage design; in other locations, both previously treated and untreated cohorts will be enrolled simultaneously.
Twenty-eight days of study drug administration is 1 cycle. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Dose modification provisions are provided in the protocol. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression, and should be scheduled within 7 days of his or her last dose of study drug, if possible. In addition to the TT visit, all subjects who discontinue acalabrutinib will have a safety follow-up visit 30 (+ 7) days after the 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. Refer to Section 4.4 for information on follow-up for progression and survival.

Intervention

protocol treatment: 100 mg BID ACP-196

Study burden and risks

not applicable

Contacts

Public
ACERTA PHARMA, BV

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NL
Scientific
ACERTA PHARMA, BV

Molenstraat 110
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

•Men and women >= 18 years of age.
• Previously treated cohort only: A confirmed diagnosis of WM, which has relapsed after, or been refractory to >= 1 prior therapy for WM and which requires treatment.
• Previously untreated cohort only: A confirmed diagnosis of previously untreated WM in subjects who require treatment and do not want to receive chemoimmunotherapy or have comorbidities that would preclude chemoimmunotherapy such as:
o Symptomatic hyperviscosity with an IgM >= 5,000 mg/dL
o Disease-related neuropathy
• Serum concentration of IgM, as measured by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), that exceeds the upper limits of normal or measurable nodal WM (defined as the presence of >= 1 lymph node

that measures >= 2.0 cm in the longest diameter and >= 1.0 cm in the longest perpendicular diameter).
• Eastern Cooperative Oncology Group (ECOG) performance status of <= 2.
• Agreement to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.7.4 .
• Agreement to refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib.
• Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
• Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

Exclusion criteria

• Prior malignancy, 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 >= 2 years or which will not limit survival to < 2 years. Note: These cases must be discussed with the medical monitor.
• A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator*s opinion, could compromise the subject*s safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.
• 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.
• 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.
• Any immunotherapy within 4 weeks of first dose of study drug.
• For subjects with recent chemotherapy or experimental therapy, the first dose of study drug must occur after 5 times the half-life of the agent(s).
• Prior exposure to a BCR inhibitor (eg, BTK, phosphoinositide-3 kinase [PI3K], or spleen tyrosine kinase [SYK] inhibitors) or B-cell lymphoma 2 (BCL-2) inhibitor (eg, ABT-199).
• Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids, for treatment of WM or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (<= 10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric

corticosteroids as needed for treatment-emergent comorbid conditions.
• Grade >= 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
• Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
• Major surgery within 4 weeks before first dose of study drug.
• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
• History of a bleeding diathesis (eg, hemophilia, von Willebrand disease)
• History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib.
• Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 28 days of first dose of study drug.
• Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
• Absolute neutrophil count (ANC) < 0.75 x 109/L or platelet count < 50 x 109/L. For subjects with disease involvement in the bone marrow, ANC < 0.50 x 109/L or platelet count < 30 x 109/L.
• Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN.
• Lactating or pregnant.
• Concurrent participation in another therapeutic clinical trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-01-2015
Enrollment:	7

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACP-196
Generic name:	ACP-196

Ethics review

Approved WMO Date:	01-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2015
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:	04-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2016

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:	19-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2023

Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	EUCTR2014-003212-36-NL
ClinicalTrials.gov	NCT02180724
CCMO	NL50257.018.14