A Phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON43776

Source
ToetsingOnline

Brief title
A Phase III trial with caplacizumab in patients with acquired TTP

Condition

- Red blood cell disorders

Synonym
Thrombotic Thrombocytopenic Purpura

Research involving

Human

Sponsors and support

Primary sponsor: Ablynx NV
Source(s) of monetary or material Support: Sponsor Ablynx NV

Intervention

Keyword: caplacizumab, phase III, TTP

Outcome measures

Primary outcome

To evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis

Secondary outcome

- to evaluate the effect of study drug on a composite endpoint consisting of TTP-related mortality, recurrence of TTP and major thromboembolic events during study drug treatment

- to evaluate the effect of study drug on prevention of recurrence of TTP over the entire study period

- to evaluate the effect of study drug on refractoriness to treatment

- to evaluate the effect of study drug on biomarkers of organ damage: lactate dehydrogenase (LDH), cardiac troponin I (cTnI), and serum creatinine

- to evaluate the effect of study drug on PE parameters (days of PE and volume), days in intensive care unit (ICU), days in hospital

- adverse events (AEs)

- pharmacodynamic (PD) markers: von Willebrand factor (vWF), coagulation factor VIII (FVIII), ristocetin cofactor activity (RICO)

- pharmacokinetic (PK) parameters

- immunogenicity (anti-drug antibodies [ADA])

Study description

Background summary

Caplacizumab (Sponsor code: ALX-0081) is intended to inhibit the interaction between von Willebrand factor (vWF) and platelets, by targeting the A1 domain of vWF. Caplacizumab selectively prevents thrombus formation in high-shear blood vessels, blocks ultra-large (UL) vWF mediated platelet interactions, and is expected not to interact with hemostasis in normal, healthy blood vessels.

Study objective

Currently, caplacizumab is being developed for treatment of acquired thrombotic thrombocytopenic purpura (TTP). TTP is a rare and potentially life-threatening thrombotic microangiopathy, in which accumulation of ULvWF multimers leads to an increased risk of thrombus formation in small blood vessels due to excessive platelet aggregation.

Study design

This is a phase III, double blind, placebo-controlled, randomized study to evaluate the efficacy and safety of caplacizumab treatment when administered in addition to standard of care treatment in subjects with an acute episode of acquired TTP. The study will evaluate the efficacy of caplacizumab in more rapidly restoring normal platelet counts and the effect of treatment with caplacizumab on a composite endpoint of TTP-related mortality, prevention of recurrence of the presenting TTP episode and prevention of major thromboembolic events during study drug treatment.
After confirmation of eligibility to study participation and after the start of PE treatment*, subjects will be randomized in a ratio of 1:1 to either receive caplacizumab or placebo in addition to standard of care therapy. Randomization will be stratified by severity of neurological symptoms (Glasgow coma scale [GCS]).

Intervention

Screening

- Obtain informed consent
- Review of eligibility criteria

- Medical history, including TTP history (and ADAMTS-13 activity levels at admission, if available)
- GCS
- Bleeding assessment
- Platelet count, blood smear, serum creatinine (local lab)
- Pregnancy test (urine or blood)
- Demographics
- Concomitant medication
- AEs

Day 1

- Randomization
- Study drug administration and PE + corticosteroids
- Platelet count, blood smear
- LDH, serum creatinine, cTnI, ADAMTS13 activity
- Complement factors C5a and C5b-9
- Assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria)
- Cognitive assessment (standardized mini mental state examination [SMMSE])
- Clinically significant TTP event
- AEs, safety laboratory parameters, physical examination, electrocardiogram (ECG), vital signs
- Concomitant medication
- Bleeding assessment
- PK, PD parameters (vWF, FVIII and RICO)
- Immunogenicity (ADA)

Study drug treatment period (including exacerbation during 30-day post daily PE period and relapse during treatment extension period), the possible treatment extension period and FU period - see Schedules of Assessments.

Study burden and risks

The following items are not part of the standard of care for this condition and are an additional burden for the study subjects associated with participation in the study: urine pregnancy test, 30 days follow up after the end of the plasma exchange with daily subcutaneous injections and weekly visits to the hospital & 2 follow-up visits after last dosing.

Contacts

Public

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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.Adult male or female * 18 years of age at the time of signing the informed consent form (ICF)
2.Clinical diagnosis of acquired TTP (initial or recurrent), which includes thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g. schistocytes)
3.Requires initiation of daily PE treatment and has received 1 PE treatment prior to randomization .

Exclusion criteria

* Platelet count *100×109/L
* Serum creatinine level >200 *mol/L in case platelet count is > 30×109/L (to exclude possible cases of atypical Hemolytic Uremic Syndrome [aHUS])
* Known other causes of thrombocytopenia including but not limited to:
- Clinical evidence of enteric infection with E. coli 0157 or related organism
- Atypical HUS

- Hematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy
- Known or suspected sepsis
- Diagnosis of disseminated intravascular coagulation
* Congenital TTP (known at the time of study entry)
* Pregnancy or breast-feeding
* Clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia)
* Known chronic treatment with anticoagulant treatment that cannot be stopped (interrupted) safely, including but not limited to:
- vitamin K antagonists
- heparin or low molecular weight heparin (LMWH)
- non-acetyl salicylic acid non-steroidal anti-inflammatory molecules
* Malignant arterial hypertension
* Clinical condition other than that associated with TTP, with life expectancy < 6 months, such as end-stage malignancy
* Subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-01-2017
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caplazicumab
Generic name:	ALX-0081

Ethics review

Approved WMO Date:	09-09-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-04-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-11-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2015-001098-42-NL
ClinicalTrials.gov	NCT02553317
CCMO	NL54235.058.15