AN OPEN-LABEL, MULTI-CENTER CONTROLLED CLINICAL TRIAL OF ECULIZUMAB IN ADOLESCENT PATIENTS WITH PLASMA THERAPY-RESISTANT ATYPICAL HEMOLYTIC-UREMIC SYNDROME (AHUS)

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Objectives: The following trial objectives for adult patients with plasma therapy-resistantAtypical Hemolytic-Uremic Syndrome (aHUS) are to:Primary:• Assess the effect of eculizumab to reduce thrombotic microangiopathy (TMA) asindicated by...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haemolyses and related conditions
Study type	Interventional

Summary

ID

NL-OMON33341

Source
ToetsingOnline

Brief title
C08-002B

Condition

- Haemolyses and related conditions

Synonym
atypical hemolytic uremic syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Alexion Pharmaceuticals
Source(s) of monetary or material Support: Alexion

Intervention

Keyword: adolescents, aHUS, eculizumab, therapy-resistant

Outcome measures

Primary outcome

Primary Endpoint:

• Platelet count change from baseline (Platelet Count Pre-PT Baseline Set-point value) after first dose of Investigational Product.

Secondary outcome

Secondary Endpoints:

• TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) during the Treatment Period compared with the TMA Intervention Rate prior to the first dose of Investigational Product;

• TMA-Event Free status defined as the absence of [1] decrease in platelet count of >25% from the Platelet Count Pre-PT Baseline Set-Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis for at least 12 weeks. Dialysis events occurring within the 14 days after the first dose of Investigational Product will not be considered as a new Treatment Period dialysis event. In addition, dialysis events that commence within the 14 days before the first dose of Investigational Product and continue up to 14 days after the first dose of Investigational Product will not be considered a new

Treatment Period dialysis event;

• Change in LDH from baseline after first dose of Investigational Product;

• Change in Quality of Life measures - EuroQol 5D from baseline after first dose of Investigational Product;

• Change in renal function parameters as assessed by change in CKD stage from baseline after the first dose of Investigational Product;

• TMA Remission;

• Safety and tolerability of eculizumab;

• PK and PD parameters during induction and maintenance phases of treatment.

Exploratory Endpoints:

• Weekly TMA-related thrombocytopenia resolution rate defined as the absence of [1] platelet count decrease > 25% from the Platelet Count Pre-PT Baseline Set Point and [2] platelet count < 150 x 109/L;

• Changes in parameters associated with intravascular hemolysis, such as in haptoglobin and schistocytes from baseline after first dose of Investigational Product;

• Changes in thrombotic marker measurements, such as D-dimer levels, fibrinopeptides 1 and 2 levels, platelet P-selectin, thrombin-anti-thrombin (TAT) complexes, neutrophils-platelet aggregates and monocyte-platelet aggregates,
from baseline after the first dose of Investigational Product;

• Changes in pro-inflammatory markers (IL-6, TNF-alpha, CRP, ESR, monocyte tissue factor, platelet tissue factor) measurements from baseline after the

first dose of Investigational Product;

• Major Adverse Vascular Events (MAVE) rate during the pre-treatment period

versus rate after the first dose of Investigational Product;

• Change in age-adjusted systolic or diastolic hypertension and

anti-hypertensive medication requirements from baseline after the first dose of

Investigational Product;

• Change in urinary protein/creatinine ratio from baseline after the first dose

of Investigational Product;

• Change in complement protein levels and/or activity such as C3, C4, C3c, C4d,

CH50, AP50, C5b-9, CFH, CFI, CFB, anti-CFH antibody values, from baseline after

first dose of Investigational Product.

Study description

Background summary

Because of the severe unmet medical need in the treatment of patients with this serious and lifethreatening rare disorder, and the demonstrated activity of eculizumab to reduce thrombotic microangiopathy (TMA); individual physicians have chosen to utilize eculizumab in the treatment of their severely affected aHUS patients. To date, there is limited clinical experience in four therapy-resistant patients, of which one young child, and one therapy-sensitive patient. These initial results in severely ill aHUS patients have generated the hypothesis to confirm whether eculizumab treatment will improve the TMA condition of patients affected by aHUS.
See also page 26 and 27 of the protocol ;7.5.1 Eculizumab in aHUS Patients

Study objective

Objectives:
The following trial objectives for adult patients with plasma therapy-resistant Atypical Hemolytic-Uremic Syndrome (aHUS) are to:
Primary:
• Assess the effect of eculizumab to reduce thrombotic microangiopathy (TMA) as

indicated by thrombocytopenia as measured by platelet count change from baseline through the treatment period in patients with plasma therapy-resistant Atypical Hemolytic-Uremic Syndrome (aHUS).

Secondary:
• Evaluate additional efficacy endpoints such as the effect of eculizumab on:
* TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) during the Treatment Period compared with the TMA Intervention Rate prior to the first dose of Investigational Product.
* TMA-Event Free status defined as the absence of [1] decrease in platelet count of >25% from the Platelet Count Pre-PT Baseline Set-Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis for at least 12 weeks.
* Key Hemolytic measures.
* Quality of Life measures.
* Renal function measures.
* TMA Remission.
• Characterize the overall safety and tolerability of eculizumab.
• Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in patients with aHUS.
• Perform a series of exploratory efficacy analyses such as the effect of eculizumab
on:
* Platelet count measures.
* Thrombotic measures.
* Pro-inflammatory markers.
* Major Adverse Vascular Events (MAVE).
* Systemic hypertension and anti-hypertensive medication.
* Additional hemolytic measures.
* Additional measures of renal function.

Study design

Patients will be treated with eculizumab for 26 weeks and will have post-treatment assessments performed at 1 week, 2 weeks, 4 weeks and 8 weeks after the last dose of eculizumab. Total trial duration for each patient is approximately 35 weeks (3-day Screening Period, 26 Week Treatment Period, 8-Week Post-Treatment Follow-up Period). The estimated duration of the study, including an estimated 6 month enrollment period is approximately 14 months. Patients may be eligible to enroll in an open-label extension study after completing study evaluations to Week 26.
Patients who prematurely discontinue investigational product during the study or who do not
enter the extension study will require follow-up contacts for 8 weeks after the last dose of
eculizumab.

Intervention

Eculizumab 900 mg or 1200 mg will be administered intravenously according to the following regimens:
• Induction Period: patients will receive eculizumab 900mg via IV infusion over approximately 35 minutes once a week (every 7 ± 2 days) for 4 weeks followed by 1200mg eculizumab for the 5th dose (7 ± 2 days) later.
• Maintenance Period: patients will receive eculizumab 1200mg via IV infusion over approximately 35 minutes every two weeks (every 14 ± 2 days).
• If the physician administers plasmapheresis, plasma exchange or FFP, 600 mg eculizumab must be administered (i) within 60 minutes after each 1 volume plasmapheresis or plasma exchange and (ii) within 60 minutes prior to each 3 units of FFP infusion, respectively.

Study burden and risks

For most patients, placements of an IV catheter and needle punctures for blood draws are usually well tolerated. However, they rarely may cause pain, bleeding, bruising, swelling, clotting, leakage of drug, and possibly infection at the needle or catheter site.
You will receive a vaccine against Neisseria meningitidis that can cause adverse reactions. Different types of meningococcal vaccines are available. Your study doctor may choose the most appropriate according to your condition. For information regarding sides effects of the vaccine you will receive, please refer to the specific leaflet of the vaccine.
The electrocardiogram is a painless procedure that traces the activity of the heart.
Plasma therapy procedures may be performed by your study doctor, at his/her discretion. The plasma for your transfusion may come from different blood supply sources depending on your medical institution. Although eculizumab is being tested for your condition, there is no guarantee that you will not be exposed to increased risks of plasma transfusion reactions after being treated with eculizumab.

Contacts

Public
Alexion Pharmaceuticals

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Scientific
Alexion Pharmaceuticals

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

1. Male or female patients from 12 and up to 18 years of age who have been diagnosed with Atypical Hemolytic-Uremic Syndrome (aHUS). Patients may be newly diagnosed, experiencing a relapse of the disease, or having a post-transplant recurrence of the disease.
2. Patients must exhibit a decrease in platelet count despite at least 4 Plasma Therapy (PT) treatments in the 1 week immediately prior to screening. At screening, platelet count must be < 150 x 10 9/L and at least 25% lower than the average of 3 platelet counts obtained during remission and at least 1 month apart over the 12 months prior to screening (designated the *average remission platelet count*).
3. If historical counts are not available, platelet count at screening must be < 75 x 10 9/L despite PT treatment administration of at least 4 PT treatments in the 1 week immediately prior to screening.
4. Known complement regulatory protein genetic abnormality, i.e., a mutation in Complement Protein 3, factor H or associated factor, factor I, or membrane cofactor protein 1 (MCP-1) or known Factor B gain-of-function mutation, or known anti-CFH antibody (*aHUS lesions*).
• Patients diagnosed with aHUS with any of these aHUS lesions are eligible and will be assigned to one of the following parallel categories during the treatment period of the trial:
* (Category 1) Complement Protein 3 or factor H or factor I functional deficiency or abnormal factor interaction (C3/CFH/CFI FFP Group);
* (Category 2) Factor B Gain of Function;
* (Category 3) Anti-CFH Antibody (Anti-CFH Group);
* (Category 4) MCP-1 deficiency (MCP-1 Group);
5. Patients diagnosed with HUS of the atypical type without documented complement regulatory protein genetic abnormality or known anti-CFH antibody are eligible if other

etiologies of HUS have been ruled out as confirmed in the Exclusion Criteria (i.e., including Shiga-toxin negative, non-infectious, non-drug-exposure-related [e.g., cyclosporine]), no known HIV positivity, and anti-phospholipid antibody negative). Thrombotic thrombocytopenic purpura also must be ruled out (i.e., ADAMTS-13 activity must be > 5%; see Exclusion Criteria). Patients meeting these conditions will be assigned to Category 5. In addition, these patients will undergo genetic testing to determine if a mutation can be identified. If a mutation is identified, the patient will be reassigned to the appropriate category.
6. Lactate dehydrogenase (LDH) level >= ULN;
7. Creatinine level >= ULN for age (patients requiring acute dialysis for acute renal failure also eligible).
8. Sexually active women of childbearing potential must be practicing an effective, reliable and medically acceptable contraceptive regimen during the entire duration of the study, including the follow-up period.
9. Patient's parents/legal guardian must be willing and able to give written informed consent and patients must be willing to give written informed assent.
10. Able and willing to comply with study procedures.

Exclusion criteria

1. ADAMTS-13 inhibitor or deficiency (i.e., ADAMTS-13 activity <5%) as measured at the screening visit.
2. Malignancy.
3. Typical HUS (Shiga toxin +).
4. Known HIV infection.
5. Identified drug exposure-related HUS.
6. Infection-related HUS.
7. Renal function status requiring chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy).
8. Patients with a confirmed diagnosis of sepsis defined as positive blood cultures within 7 days of the screening visit and not treated with antibiotics to which the organism is sensitive.
9. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.
10. Pregnancy or lactation.
11. Unresolved meningococcal disease.
12. Known Systemic Lupus Erythematosus (SLE) or antiphospholipid antibody positivity or syndrome.
13. Any medical or psychological condition that, in the opinion of the investigator, could increase the patient*s risk by participating in the study or confound the outcome of the study.
14. Patients receiving IVIg or Rituximab therapy.
15. Patients receiving other immunosuppressive therapies such as steroids, mTOR inhibitors or FK506 inhibitors are excluded unless: [1] part of a post-transplant anti-rejection regime, [2] patient has confirmed anti-CFH antibody requiring immunosuppressive therapy and [3]

dose of such medications have been unchanged for at least 4 weeks prior to the screening period.
16. Patients receiving Erythrocyte Stimulating Agents (ESAs) unless already on a stable dose for at least 4 weeks prior to the screening period.
17. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedures beginning 4 weeks prior to screening and throughout the entire 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):	09-03-2010
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	eculizumab
Generic name:	Soliris
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-03-2009

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-08-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-11-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2008-006953-41-NL
ClinicalTrials.gov	NCT00844844
CCMO	NL27276.091.09