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Cemdisiran and eculizumab dose-ranging study for paroxysmal nocturnal haemoglobinuria

Submission date
24/04/2019

Recruitment status
Stopped

Registration date
15/05/2019

Overall study status
Stopped

Last Edited
06/10/2021

Condition category
Haematological Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare blood condition where blood cells are likely to be attacked by part of the body's immune system. The process where the red blood cells are destroyed is called haemolysis and it is responsible for many of the symptoms of the disease. Treatment for patients with PNH is often lifelong and can be inconvenient with time off work/education for eculizumab infusions. Patients receiving eculizumab have an infusion every 2 weeks (after the initial 4 weekly doses). Cemdisiran is a new drug made by the pharmaceutical company, Alnylam, which stops the production of C5 protein, which then stops the terminal complement pathway (part of the immune system) and may reduce haemolysis and disease symptoms. This will be given with eculizumab, which patients will already be receiving. This study will assess cemdisiran and eculizumab being given at varying doses either every 4 weeks or every 8 weeks. By spacing out the infusions, patients will have longer periods of time between treatment and this could be a great benefit for patients. Reducing the frequency (and possibly the dose) could also help save the NHS money. This study will also help us learn more about giving cemdisiran and eculizumab together.

Who can participate?
Patients at least 18 years old with a diagnosis of PNH and on eculizumab therapy for a minimum of 90 days at a stable dose of 900mg (i.e. the dose of eculizumab has not changed in the previous 90 days). Patients (and partners of patients) must be willing to use a highly effective method of contraception. Patients must be willing and able to comply with the requirements of the study and provide written informed consent. Patients must have been vaccinated against Neisseria meningitidis according to standard practice.

What does the study involve?
Participants are registered into groups of three and this allocation determines what dose and schedule of cemdisiran and eculizumab they receive. Participants attend for a screening visit and then if they are eligible, they attend for some tests and receive the first dose of cemdisiran. Patients are then seen one week before their second dose of cemdisiran is due, so either at week 3 for patients on 4 weekly treatment or week 7 for patients on 8 weekly treatment.

Patients then attend for treatment, either every 4 weeks or every 8 weeks. A number of tests and blood samples are taken at these visits to monitor the disease. Treatment is given for 32 weeks and there is an end of treatment visit at week 36.

What are the possible benefits and risks of participating?
Information gained from this study will help researchers learn about the combination of cemdisiran and eculizumab. Participants will have fewer treatment infusions than they normally would and this could possibly benefit patients in the future. As cemdisiran has only been given to six PNH patients in another trial, the potential side effects are not yet known. Patients will be monitored regularly whilst receiving study treatment and any side effects will be monitored closely. Participating in this study would involve more visits to hospital than standard care as patients would need to attend every 4 or 8 weeks (depending on which group they are registered into at the start of the trial) to receive the trial drugs. The blood tests may cause some bleeding and pain. The doctors and nurses may be able to give some treatment to help with these. This would be the same as if participants were receiving standard treatment. Cemdisiran is given by subcutaneous injections which can cause mild discomfort. Eculizumab is given by intravenous infusion (into the vein) which can cause discomfort or bruising. Participants on eculizumab are at a higher risk of infections so patients must have had meningococcal vaccination before starting trial treatment (this will have been given before starting eculizumab). It is also recommended that participants take prophylactic antibiotics to further protect against this risk.

Where is the study run from?
This study is being organised by the Clinical Trials Research Unit (CTRU) at the University of Leeds with patients being seen at St James's University Hospital, Leeds (UK)

When is the study starting and how long is it expected to run for?
April 2018 to June 2021

Who is funding the study?
Alnylam Pharmaceuticals, Inc. (USA)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-000816-27

Protocol serial number
HM19/121434

Study information

Scientific Title
A phase II, dose-ranging study in patients with Paroxysmal noctuRnal haemoglobINuria, treated with Cemdisiran and Eculizumab

Acronym
PRINCE

Study objectives
The primary objective is to determine a sufficiently effective dose and schedule of eculizumab in combination with cemdisiran.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/03/2020, South Central - Oxford C Research Ethics Committee (Level 3, Block B, Whitefriars Building, Lewins Mead, Bristol BS1 2NT, UK; +44 (0)207 104 8241; oxfordc.rec@hra.nhs.uk), REC ref: 19/SC/0453

Primary study design
Interventional

Study design
Phase II single-centre open-label study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Paroxysmal nocturnal haemoglobinuria (PNH)

Interventions
Participants will be registered into the trial in cohorts and will receive cemdisiran and eculizumab. The dose and frequency of the drugs will depend on which cohort a patient is registered into.

Eculizumab is the standard treatment for patients with PNH and is given intravenously. Cemdisiran is the new treatment and is given subcutaneously. The cohorts are:

A - cemdisiran 600 mg every 8 weeks and eculizumab 600 mg every 8 weeks
B - cemdisiran 600 mg every 8 weeks and eculizumab 900 mg every 8 weeks
C - cemdisiran 600 mg every 4 weeks and eculizumab 300 mg every 4 weeks
D - cemdisiran 600 mg every 4 weeks and eculizumab 600 mg every 4 weeks

Patients will attend for a screening visit and then if they are eligible, they will attend for some baseline tests and receive the first dose of cemdisiran. Patients will then be seen one week before their second dose of cemdisiran is due, so either at week 3 for patients on 4 weekly treatment or week 7 for patients on 8 weekly treatment. Patients will then attend for treatment either every 4 weeks or every 8 weeks. A number of tests and blood samples will be taken at these visits to monitor the disease. Disease control is monitored for the first 8 weeks in order to determine subsequent dosing. Treatment will be given for 32 weeks and there will be an end of treatment visit at week 36.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Eculizumab, cemdisiran

Primary outcome(s)
Disease control up to 8 weeks, defined by LDH ≤1.5 × upper limit of normal (ULN) maintained up to 8 weeks with treatment at allocated dose schedule, measured by blood results

Key secondary outcome(s)
1. The changes in LDH in patients with PNH over the course of the study:
1.1. LDH ≤1.5 × ULN maintained up to 36 weeks, measured by blood results
1.2. LDH levels at each of the scheduled timepoints up to 36 weeks, measured by blood results
2. The safety, tolerability and compliance of cemdisiran in combination with eculizumab administration:
2.1. Incidence of adverse events (AEs), from consent until 28 days post last dose of trial treatment:
2.1.1. Number of haemoglobinuria events, measured by blood results
2.1.2. Number of transfusions per participant, reported by the participant
2.2. Treatment compliance, measured throughout the study:
2.2.1. Dose modifications to registered treatment schedule including reasons, reported by the research team

Completion date
01/03/2022

Reason abandoned (if study stopped)
The study did not open to recruitment due to COVID-19 restrictions

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 30/07/2019:
1. Aged at least 18 years
2. Diagnosis of PNH and on eculizumab therapy for a minimum of 90 days at a stable dose (i.e. the dose of eculizumab has not changed in the previous 90 days)
3. Women of child-bearing potential1 (WOCBP) must have a negative pregnancy test, cannot be breastfeeding, and must be willing to use a highly effective method of contraception 14 days before cemdisiran administration, throughout study participation, and for 6 months after cemdisiran administration
4. Male participants with partners that are WOCBP must use double-barrier contraception (male condom plus appropriate barrier method for the female partner) for 14 days before cemdisiran administration, throughout study participation, and for 6 months after cemdisiran administration. Male participants must not donate sperm while on treatment and for at least 6 months after last dose of cemdisiran
5. Willing and able to comply with the study requirements and to provide written informed consent
6. Vaccinated against Neisseria meningitidis according to standard practice

Previous participant inclusion criteria:
1. Aged at least 18 years
2. Diagnosis of PNH and on eculizumab therapy for a minimum of 90 days at a stable dose of 900mg (i.e. the dose of eculizumab has not changed in the previous 90 days)
3. Women of child-bearing potential1 (WOCBP) must have a negative pregnancy test, cannot be breastfeeding, and must be willing to use a highly effective method of contraception 14 days before cemdisiran administration, throughout study participation, and for 6 months after cemdisiran administration
4. Male participants with partners that are WOCBP must use double-barrier contraception (male condom plus appropriate barrier method for the female partner) for 14 days before cemdisiran administration, throughout study participation, and for 6 months after cemdisiran administration. Male participants must not donate sperm while on treatment and for at least 6 months after last dose of cemdisiran
5. Willing and able to comply with the study requirements and to provide written informed consent
6. Vaccinated against Neisseria meningitidis according to standard practice

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Key exclusion criteria
1. Alanine transaminase (ALT) ≥2 ×ULN, or total bilirubin ≥4×ULN (unless bilirubin elevation is due to Gilbert's syndrome), and considered clinically relevant in the opinion of the Investigator
2. Spontaneous vascular thrombosis within 90 days of registration (patients may be rescreened)
3. History of bone marrow transplantation
4. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
5. Planned change in eculizumab dose within 90 days of administration of cemdisiran (patients may be rescreened)
6. Known or suspected hereditary asymptomatic complement deficiency
7. Known clinical laboratory evidence or clinical diagnosis of human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, or chronic hepatitis B virus (HBV) infection as shown by hepatitis B surface antigen positivity in the blood
8. Presence or suspicion of active viral, bacterial, fungal, or parasitic infection within 14 days before cemdisiran administration (patients may be rescreened)
9. Travelled to Saudi Arabia or Africa within 90 days of Screening, or planning to do so during the study (patients may be rescreened)
10. Received a complement targeted investigational agent within 90 days prior to screening (or 5 half-lives) depending which is longer
11. In follow-up of another clinical trial before trial registration
12. Active serious mental illness or psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention
13. Other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
14. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc)
15. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
16. History of meningococcal infection within 12 months before screening
17. Known history or evidence of chronic liver disease, alcohol abuse or cirrhosis
18. Concomitant use of anticoagulants if not on a stable dose regimen for at least 2 weeks prior to screening
19. Significant aplasia e.g. neutrophils <0.5 x 10*9/l or platelets <30 x 10*9/l

Date of first enrolment
01/04/2020

Date of final enrolment
01/07/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

St James's University Hospital
Department of Haematology
Level 3, Bexley Wing
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Alnylam Pharmaceuticals

Alternative Name(s)
Alnylam, Alnylam Pharmaceuticals, Inc

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete.

Data will be shared according to a controlled access approach, based on the following principles:
1. The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
2. The researchers encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets
3. The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team.
4. Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. The researchers will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. They will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
5. Any data release must be in line with any contractual obligations to which the CTRU is subject
6. The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project
7. The research project must have clear objectives and use appropriate research methods
8. The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure

Participants in this trial have not given explicit consent for their data to be shared for secondary research. However, they were provided with notification at trial entry of our intention to make data available for further research. In addition, data will only be made available in such a way that data recipients cannot identify individuals by any reasonably likely means, and the researchers will only share data for projects that are clearly in the public interest and compatible with the original purpose of the data processing.

Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No