A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Published: 25-02-2021
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-507977-16-00 check the CTIS register for the current data. To evaluate the efficacy of ravulizumab compared with placebo to reduceproteinuria in adult participants with LN or IgAN.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON54071

Source
ToetsingOnline

Brief title
ALXN1210-NEPH-202

Condition

- Nephropathies

Synonym
Berger's disease, Kidney disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Immunoglobulin A Nephropathy (IgAN), Lupus Nephritis (LN)

Outcome measures

Primary outcome

-Percentage change in proteinuria

Secondary outcome

Common to both disease cohorts: - Percentage change in proteinuria - Change from baseline in eGFR For LN: - Percentage of participants meeting the criteria for Complete Renal Response - Percentage of participants meeting the criteria for Partial Renal Response - Time to UPCR (Urine Protein to Creatinine Ratio) < 0.5 g/g - Percentage of participants achieving corticosteroid taper to 7.5 mg/day - Percentage of participants with Renal Flare - Percentage of participants with Extrarenal SLE (Systemic Lupus Erythematosus) Flare -Percentage of participants with Suboptimal Response through Week 50 For IgAN: - Percentage of participants meeting the criteria for Partial Remission

Study description

Background summary

Lupus nephritis occurs in approximately 50% of patients with systemic lupus erythematosus (SLE), an autoimmune disorder caused by loss of tolerance to

self-antigens, the production of autoantibodies, and deposition of complement-fixing immune complexes (ICs) in injured tissues (Bao, 2015). The diagnosis of LN is determined by kidney biopsy according to the 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) nomenclature and classification revised from the 2003 report (Bajema, 2018; Markowitz, 2007). In total there are 6 classes of LN: Classes I to VI (Markowitz, 2007). The subset of patients with SLE that develop LN have the worst prognosis (Hoover, 2016). Lupus nephritis leading to CKD is an independent major risk factor for overall mortality and morbidity attributed to cardiovascular disease and
septic shock. With current induction and maintenance therapies, the 5-year mortality is approximately 20% and the risk of developing ESRD at 5, 10, and 15 years are 11%, 17%, and 22%, respectively (Mageau, 2019). Recurrence of LN after treatment (renal flare) occurs within
1 year in up to 25% of patients and is associated with increased risk of CKD progression (Almaani, 2017).

The pathophysiology of LN involves multiple overlapping pathways where complement serves as a mediator of an abnormal immune response (Bao, 2015; Pickering, 2000; Schur, 1988). The terminal complement components (C5a and terminal complement complex [C5b-9]) trigger acute
cellular inflammatory responses through activation of interleukin and cytokine signaling. Complement also serves to fix immunoglobulins and ICs in the kidney. In fact, complement and complement split products are a prominent histologic finding in kidney biopsies of LN (Biesecker, 1981; Wilson, 2019). Serum levels of these autoimmune and complement biomarkers are linked with disease activity (Birmingham, 2015; Dall*Era, 2011). Decreases in complement components 3, 4, and 1q (C3, C4, and C1q) are associated with de novo LN and LN flares. Likewise, levels of complement biomarkers correlate with disease activity in SLE (Kim, 2019). Restoring complement regulation may improve renal responses through acute anti-inflammatory effects and lasting effects on IC deposition in the kidney. Thus, anti-C5 therapy is promising for both induction treatment for active proliferative LN and maintenance treatment of chronic LN.

The American College of Rheumatology (ACR), and joint recommendations from the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), recommend immunosuppression treatment for Class III,
IV, III/V, and IV/V LN also called *proliferative* LN (Bertsias, 2012). The guidelines agree on induction treatment with glucocorticoids plus mycophenolate mofetil (MMF) or cyclophosphamide. For maintenance therapy, the guidelines agree on MMF or azathioprine, with
or without low dose glucocorticoids. In patients with LN, the main goal of therapy is prevention of CKD progression, ESRD, and death. Lack of achievement of remission, in particular complete remission, is one of the major risk factors for progression of renal disease. Hence, short-term
complete and partial renal remissions are used to assess the efficacy of

standard of care and novel therapies. However, after 6 to 12 months of treatment, only 10% to 40% of patients achieve a Complete Renal Response (CRR) with standard of care (Parikh, 2016).

Study objective

This study has been transitioned to CTIS with ID 2023-507977-16-00 check the CTIS register for the current data.

To evaluate the efficacy of ravulizumab compared with placebo to reduce proteinuria in adult participants with LN or IgAN.

Study design

Study ALXN1210-NEPH-202 is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in addition to background therapy consistent with the standard-of-care in 120 adult participants (18 to 75 years of age) with either LN or IgAN. All participants must be naive to complement inhibitor treatment and have either a diagnosis of LN with an active flare or IgAN based on kidney biopsy, estimated glomerular filtration rate (eGFR) >= 30 mL/min/1.73m2, and proteinuria [defined as urine protein to creatinine ratio (UPCR) >= 1 g/g from one 24-hr urine collection (LN cohort) or as mean protein >= 1 g/24-hr from 2 valid 24-hr collections (IgAN cohort)]. Participants in the IgAN cohort must have been treated with stable doses of the maximum tolerated renin-angiotensin system (RAS)-inhibiting medications and have controlled, stable blood pressure (< 140/90 mmHg) for >= 3 months prior to Screening. Approximately 60 participants in each disease cohort will be randomly assigned in a 2:1 ratio to receive ravulizumab or placebo (40 ravulizumab, 20 placebo). Randomization will be stratified by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period for participants in the LN cohort and by mean proteinuria (1 to 2 g/day versus > 2 g/day) from 2 valid 24-hr urine collections during Screening Period for participants in the IgAN cohort. The study consists of an up to 6-week Screening Period, a 26-week Initial Evaluation Period, a 24-week Extension Period, and a 36-week post-treatment Follow-up Period.

Intervention

Ravulizumab is formulated at pH 7.0 and is supplied in 30 mL single-use vials. Each vial of ravulizumab contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. The comparator product (placebo) is formulated as a matching sterile, clear, colorless solution with the same buffer components, but without active ingredient.

The dosing regimen consists of a loading dose followed by maintenance dosing administered q8w. The maintenance dosing will be initiated 2 weeks after the loading dose administration. Weight-based dosing will be based on the participant*s body weight recorded at the day of the
infusion visit. If the weight at the day of the infusion cannot be obtained, the weight recorded during the most recent prior study visit may be used.

During the Initial Evaluation Period (Day 1 through Week 26), participants in each cohort will be randomized 2:1 to receive blinded doses of ravulizumab or placebo.
- Ravulizumab group: participants will receive a blinded loading dose of ravulizumab via IV infusion on Day 1, followed by a blinded maintenance doses at Week 2 then q8w thereafter through the end of the Initial Evaluation Period
- Participants in the placebo group will receive a blinded matching placebo dose via IV infusion on Day 1, followed by a blinded matching placebo dose at Week 2, then q8w thereafter through the end of the Initial Evaluation Period.

During the Extension Period (Week 26 through Week 50), participants in the LN cohort will continue on the same maintenance regimen. In the IgAN cohort, participants in the placebo group will switch to receive a blinded loading dose of ravulizumab at Week 26 and participants in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 26. Starting at Week 28, all participants in the IgAN cohort will receive open-label weight-based doses of ravulizumab (Table 9) q8w until the end of the Extension Period.

Study burden and risks

-The study will take about 86 weeks in total for patients.
-Additional visits to the hospital
-Extra physical exams and pregnancy testing
-Around 468 mL blood will be taken. This amount won't cause any problem (to compare: A blood donation involves 500mL of blood tests. Possible side effects of blood draws are are fainting, confisions, sore spot and sensitive area at the injection site and, in rare cases, an infection.
-Meningococcal Infection: Patients receiving the study drug, even after a single dose, are at increased risk of developing serious infections caused by the bacteria Neisseria meningitidis. The infection can affect the tissues that surround the brain and spinal cord (meningococcal meningitis) or can develop in the blood (meningococcal sepsis). Meningococcal infections can rapidly become life-threatening or fatal. It is very important that the infection is diagnosed and treated early. If patients have not been vaccinated recently, they will be given a vaccine to protect against the bacteria that causes meningococcal infections. Vaccination alone may not be sufficient to prevent infection with Neisseria meningitidis. The study doctor may also prescribe antibiotics to help protect patients from infection.
-Possible rash or superficial irritation of the skin by the ECG stickers.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Common to both disease cohorts: - 18 - 75 years of age - Proteinuria >= 1 (g/d or g/g) - Vaccinated against meningococcal infection - Vaccinated against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae For LN cohort: - Diagnosis of active focal or diffuse proliferative LN Class III or IV - Clinical active LN, requiring/receiving immunosuppression induction treatment For IgAN cohort: - Diagnosis of primary IgAN - Compliance with stable and optimal dose of RAS inhibitor treatment for >= 3 months - For participants with a kidney biopsy used for eligibility > 1 year prior to Screening : Presence of hematuria as defined by a positive result on urine dipstick for blood or >= 10 red blood cell (RBC)/hpf microscopy on urine sediment (as documented by the local laboratory). Presence of hematuria documented by the central laboratory may also be acceptable. Participants with established intolerance to RAS

inhibitors may be included

Exclusion criteria

Common to both disease cohorts: - Estimated GFR < 30 mL/min/1.73 m2 - For patients with eGFR < 45 mL/min/1.73 m2 at Screening, presence of any of the following in glomeruli on most recent kidney biopsy prior or during the Screening Period: >= 50% interstitial fibrosis and tubular atrophy >= 50% glomerular sclerosis, >= 50% active crescent formation - Previously received a complement inhibitor (eg, eculizumab) at any time - Concomitant significant renal disease other than LN or IgAN - History of other solid organ or bone marrow transplant - Uncontrolled hypertension - Institutionalization by administrative or court order or known medical or psychological condition or risk factor that, in the opinion of the Investigator, might interfere with the participant's full participation in the study. Known history of humane immunodeficiency virus (HIV) infection - Hypersensitivity to any ingredient contained in the study drug For LN cohort: -Participants who have initiated any of the following treatments for the current active LN flare : a. Cyclophosphamide <= 6 months prior to Screening b. Calcineurin inhibitors <= 3 months prior to Screening c. A cumulative dose of IV methylprednisolone > 3 g d. Mycophenolate mofetil > 2 g/day (or equivalent) for >= 4 consecutive weeks prior to Screening e. Oral corticosteroids >= 0.5 mg/kg/day for >= 4 consecutive weeks prior to Screening For IgAN cohort: - Diagnosis of rapid progressive glomerulonephritis - Prednisone or prednisone equivalent > 20 mg/day for > 14 consecutive days or any other systemic immunosuppression for the treatment of IgAN <= 6 months prior to Screening -Body mass index >=38 kg/m2

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-01-2022
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ravulizumab
Generic name:	Ravulizumab

Ethics review

Approved WMO Date:	25-02-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-07-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-02-2022

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-06-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
EU-CTR	CTIS2023-507977-16-00
EudraCT	EUCTR2020-001537-13-NL
CCMO	NL75823.068.21