A Multicenter Randomized Double-Blind Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Anifrolumab in Adult Patients with Active Proliferative Lupus Nephritis

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This study has been transitioned to CTIS with ID 2023-506359-68-00 check the CTIS register for the current data. This study investigates the safety and efficacy of the new drug anifrolumab in patients with Lupus Nephritis. The effect of anifrolumab...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON51523

Source
ToetsingOnline

Brief title
IRIS

Condition

- Autoimmune disorders
- Renal disorders (excl nephropathies)

Synonym
inflammation kidney due to auto-immune disease

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Sponsor: AstraZeneca

Intervention

Keyword: Active Proliferative Lupus Nephtritis, Anifrolumab

Outcome measures

Primary outcome

CRR at Week 52, ie, meeting all of the following:

• UPCR <= 0.5 mg/mgb

• eGFR >= 60 mL/min/1.73 m2 or no decrease from baseline of >= 20%

Secondary outcome

- Sustained OCS reduction, ie, meeting all of the following:

• OCS dose of <= 7.5 mg/day prednisone or equivalent by Week 24

• Sustained OCS dose of <= 7.5 mg/day prednisone or equivalent from Week 24

through Week 52

- Time to sustained CRR (see above; ie, time from first study intervention dose

to achieving CRR that is sustained from that time point through Week 52)

- Cumulative UPCR as determined by the standardized AUC from baseline up to and

including Week 52

- Time to renal event as defined as any of the following:

1) Early Stage Kidney Disease, 2) doubling of serum creatinine, 3) renal

worsening as evidenced by increased proteinuria and/or renal function

impairment, or 4) renal disease treatment failure or death

Study description

Background summary

Lupus nephritis (LN) is an inflammation of the kidneys ("nephritis") caused by the disease systemic lupus erythematosus (SLE). SLE is a disease of the body's immune system. The immune system protects the body against germs, such as bacteria and viruses, but in SLE the immune system attacks its own organs. In these organs inflammation develops. In about half of SLE patients, the kidneys are damaged. As a result, protein and blood cells leak into the urine and the functioning of the kidneys deteriorates.
Current standard treatment aims to reduce symptoms and slow down the deterioration of renal function. However, there is a need for new drugs that are more effective and/or safer than current treatment.
Anifrolumab is a monoclonal antibody specially made in the laboratory to block the effect of certain parts of the immune system (so-called type 1 interferons). These interferons most likely play a role in LN. Blockage of the interferons with anifrolumab reduces the inflammatory response in the kidneys. It is expected that the symptoms will also decrease as a result. Anifrolumab has been tested in medical-scientific tests as a treatment against SLE, with and without LN.
Anifrolumab has not yet been approved by the Dutch government. Doctors are not yet allowed to prescribe the drug to patients. Anifrolumab has been registered in the United States since August 2021 for the treatment of adults with SLE as an adjunct to standard treatment.
The standard treatment for LN used in this study consists of mycophenolate mofetil (abbreviated as MMF) and steroids, such as prednisone. MMF and steroids are registered in the Netherlands for other treatments, but not for the treatment of LN. Yet they are often used for the treatment of LN.

Study objective

This study has been transitioned to CTIS with ID 2023-506359-68-00 check the CTIS register for the current data.

This study investigates the safety and efficacy of the new drug anifrolumab in patients with Lupus Nephritis. The effect of anifrolumab is compared with the effect of a placebo. Anifrolumab and placebo ("the study drug") are added to the usual treatment ("the standard treatment") for lupus nephritis during this study.

- Primary Objective:
To evaluate the efficacy of anifrolumab compared with placebo as added to SOC in active proliferative LN on the proportion of participants achieving CRR

- Key Secondary Objectives:
To evaluate the effect of anifrolumab as compared with placebo as added to SOC on:
* Sustained OCS reduction
* Onset of sustained CRR
* Proteinuria
* Onset of renal-related event or death through Week 52
Onset of renal-related event or death through Week 76

For all objectives, see Table 4 in the protocol.

Study design

This is a phase 3 randomized double-blind placebo-controlled study investigating the efficacy and safety of anifrolumab in adult patients with active proliferative lupus nephritis.

Intervention

Approximately 360 participants will be randomized in a 1:1 ratio to receive anifrolumab 900 mg IV Q4W for the first 6 doses (Weeks 0 to 20) and 300 mg IV Q4W for the remainder of the study, or matching placebo throughout during the Treatment Period. Randomization will be stratified using the following factors:
- UPCR > 3 vs <= 3 mg/mg
- New onset vs relapsing LN
- Race (White vs not White)

Study burden and risks

Patients will need to come to the hospital more often and visits will be longer than usual. Patients will undergo the following examinations during the study:
- Discussion of medical history.
- Discussion of general health, any symptoms that may indicate a corona and/or tuberculosis infection and any mental problems (e.g. depression). Discussion of the drugs being used. A number of questions have to be answered on a tablet.
- Physical examination.
- Check blood pressure, pulse, respiration rate, temperature, height and weight.
- Blood tests (including tests for TB, inflammation of the liver [hepatitis] and HIV). Approximately 585 ml of blood will be collected during the entire study.
- Saliva or swab for coronavirus research.
- Urinalysis (24 hour urine and first morning urine).

- Pregnancy Test
- ECG
- X-ray or CT scan of the lungs.
- cervical cancer screening: This examination may not need to be done if it has been done in the past 2 years and the result is available and not abnormal. If the participant is under 25 years of age and has no sexual activity, or if the participant has had an HPV vaccination, a Pap/HPV test may not be required.
- Kidney biopsy. This survey does not need to be done if it has been done within the past 6 months.
- Filling in questionnaires about general health, about depression and thoughts of suicide, corona and about TB.

This study includes:
- Screening Period: Up to 30 days
- Treatment Period: 76-weeks - Study visits will take place every 4 weeks (+/- 7 days).
- open label period: 52 weeks - Study visits will take place every 4 weeks (+/- 7 days).
- Follow-up Period: After the last administration of the study medication/placebo, two follow-up visits will take place (4 weeks and 8 weeks after the last administration of the study medication/placebo).

Possible side effects of anifrolumab:
As of 18 January 2020, 1030 patients have received at least one dose of the study drug
in the ongoing clinical studies.
- The most common side effects (in more than 3% patients) that have been reported in patients receiving the study drug are: cold (nasopharyngitis), infection of the upper airways,urinary tract infection,infusion-related reaction,headache, shingles, back pain, cough, joint pain, infection of sinuses (cavities around nose and head), vomiting, nausea, cold sore, allergic reaction, loose motions (diarrhoea), infection of the intestine (gastroenteritis), acid reflux (gastroesophageal reflux disease), stomach pain, difficulty falling asleep (insomnia), increased blood pressure.
- The serious side effects that have been reported in 2 or more patients receiving the study drug are: pneumonia, swelling under the skin (angioedema), appendicitis, asthma, chest pain, infection of intestine.

Possible risks with MMF
- Serious infections and cancer: MMF is a so-called immunosuppressant medication (a medication that dampens your immune system and therefore can reduce your body*s ability to fight off infections). For this reason, MMF can increase the risk of different types of infections. In the worst case, this can lead to serious complications or on rare occasions even to death. MMF can also increase the risk of certain types
of cancers.
- Blood cells: MMF can sometimes affect the number of certain cells in your

blood, for example cells that are important to fight off infections (so-called white blood cells) and also cells that function to transport oxygen to your body (so-called red blood cells).
- Stomach and intestine: Treatment with MMF can sometimes lead to ulcers or bleeding from your stomach or intestines and in very rare cases cause problems (inflammation) in an organ called pancreas that is important for food digestion.
- Pregnancy and breast-feeding: MMF increases the risk for early pregnancy loss and can also harm the newborn child (cause birth defects). This can happen both when the mother or the father of the child is taking MMF. If a breast-feeding mother is taking MMF the medicine can be present in the breast milk an cause harm to the baby.

Risks from study procedures:
There are potential risks associated with some of the study procedures you will have in this study.
- Anifrolumab or placebo administration: potential risks from receiving study drug through administration into a vein are infection, redness, swelling, pain, and hardening of the tissue where you received it.
- Blood collection: When blood is taken, this might cause some pain or discomfort, and afterwards one may have a bruise in the area where the sample was taken. Both the discomfort and bruising should disappear in a few days. One may also experience dizziness, nausea, or fainting when blood samples are taken.
- Pap smear test: For females a Pap smear test or hpv test will be done. The doctor will use an instrument to see your cervix. This may cause a sensation of pressure in the pelvic area. One may also experience a small amount of bleeding after the test is performed. The Pap smear test may result in additional appointments and time spent.
- Electrocardiogram (ECG): There may be mild discomfort from the pads when removed, and the skin may be irritated by the adhesive on the pads. Some hair may need to be shaved before placement of the pads.
- Chest x-ray: The x-ray will involve being exposed to more radiation than usual. Every day we are exposed to natural background radiation and some things that we do increases our exposure to radiation (for example, being on a flight). The additional radiation from the chest x-ray will not exceed the level of 1 year of natural background radiation.

Contacts

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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. Age 18 through 70 years at the time of Screening. 2. Fulfills updated 2019 SLE criteria. 3. Positive ANA, anti-dsDNA, or anti-Sm test result in sample obtained during Screening. 4. Urine protein to creatinine ratio > 1 mg/mg (113.17 mg/mmol) (mean of 2 spot UPCR [FMV] samples obtained during Screening). 5. Active proliferative LN Class III or IV either with or without the presence of Class V (excluding pure Class III[C], IV-S[C], or IV-G[C]) according to the 2003 ISN/RPS classification based on a renal biopsy obtained within 6 months prior to signing the ICF or during Screening Period. 6. eGFR >= 35 mL/min/1.73 m2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula). 7. Adequate peripheral venous access. 8. Chest radiograph (obtained during Screening or within 12 weeks prior to signing of the informed consent) or a CT scan of the chest (within 12 weeks of signing the informed consent) that meets all of the following criteria: No evidence of current active infection (eg, pneumonia, TB) or previous TB; No evidence of malignancy; No CS abnormalities (unless due to SLE). 9. Meets all of the following TB criteria: No signs or symptoms of active TB prior to or during any Screening visit; No medical history or past physical examinations suggestive of active TB; A chest radiograph during the Screening Period or within 12 weeks prior to signing the ICF with no evidence of active or signs of prior TB infection; No recent contact with a person with active TB OR if there has been such contact,

referral to a physician specializing in TB to undergo additional evaluation prior to Week 0 (Day 1) (documented comprehensively in source) and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of study intervention; No history of latent TB prior to signing the ICF, with the exception of latent TB with documented completion of appropriate treatment.The participant must undergo an IGRA (eg, QFT-G test) test for TB obtained from the study central laboratory at Screening with results in line with protocol specified rules. 10. Negative SARS-Cov-2 RT-PCR test result at Screening and no known or suspected COVID-19 infection or exposure between signing the ICF and Week 0 (Day 1). There must be a minimum of 2 weeks between the 2 tests at Screening and Week 0 (Day 1). 11. Body weight >= 40.0 kg. 12. Females with an intact cervix must have documentation of a Pap smear with no documented malignancy (eg, CIN III, carcinoma in situ, or adenocarcinoma in situ) within 2 years prior to Week 0 (Day 1) 13. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (as described in protocol).

Exclusion criteria

1. A diagnosis of pure Class V LN based on the renal biopsy obtained within 6 months prior to signing the ICF or during Screening. 2. History of dialysis within 12 months prior to the ICF or expected need for renal replacement therapy (dialysis or renal transplant) within a 6-month period after enrollment. 3. History of, or current renal diseases (other than LN) that, in the opinion of the Investigator, could interfere with the LN assessment and confound the disease activity assessment (eg, diabetic nephropathy) 4. History of recurrent infection requiring hospitalization and/or IV antibiotics (eg, 2 or more of the same type of infection over the previous 52 weeks). 5. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection, or a positive result for HIV confirmed by the central lab at Screening - an HIV test must be performed during Screening, and the result should be available prior to Week 0 (Day 1). 6. At Screening, confirmed positive test for hepatitis B serology, as confirmed by central lab, for: HBsAg or HBcAb and HBV DNA detected above the LLOQ by reflex testing by the central lab at Screening. Participants who are HBcAb positive at Screening will be tested every 3 months for HBV DNA. To remain eligible for the study, the participant*s HBV DNA levels must remain below the LLOQ as per the central lab. 7. Positive test for hepatitis C antibody as confirmed by the central lab. 8. Any severe case, as defined by study guidelines, of HZ infection at any time prior to Week 0 (Day 1). 9. Any clinical CMV or EBV infection that has not completely resolved within 12 weeks prior to the ICF. 10. Opportunistic infection (see Section 8.3.8.2 of protocol) requiring hospitalization or IV antimicrobial treatment within 3 years prior to the ICF. 11. Clinically significant chronic infection (ie, osteomyelitis,

bronchiectasis, etc) within 8 weeks prior to signing the ICF (chronic nail infections are allowed) or any infection requiring hospitalization or treatment with IV anti-infectives not completed at least 4 weeks prior to the ICF. 12. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to Week 0 (Day 1). 13. History of cancer, apart from: Squamous or basal cell carcinoma of the skin treated with documented success of curative therapy >= 3 months prior to Week 0 (Day 1); Cervical cancer in situ treated with apparent success with curative therapy >= 1 year prior to Week 0 (Day 1). 15. Prior receipt of anifrolumab. 16. Previous receipt of >*2 investigation treatments (other than anifrolumab) for LN or SLE since time of diagnosis and through the ICF. 17. Known intolerance to <= 1.0 g/day of MMF. 18. Receipt of any commercially available biologic agent within 5 half-lives (see Appendix O for a complete list) prior to signing of the ICF. 19. Receipt of any of the following prior to signing the ICF (refer to Appendix O of protocol for a complete list): Receipt of B cell-depleting therapy <= 26 weeks prior to the ICF or if therapy was administered > 26 weeks ago, if absolute B cell count is below the lower limit of normal or is baseline value prior to receipt of B cell-depleting therapy (whichever is lower) 20. A known history of allergy or reaction to any component of the study intervention formulation or history of anaphylaxis to any human gamma globulin therapy, human proteins, or monoclonal antibodies. 21. Receipt of any of the following: - Any live or attenuated vaccine within 8 weeks prior to signing the ICF (killed vaccines are acceptable) - Any restricted medication listed in Appendix O not discontinued according to the prescribed timeframe prior to ICF - Blood transfusion within 4 weeks prior to signing the ICF - Any of the following for the current LN flare (ie, since the qualifying renal biopsy): IV cyclophosphamide > 2 pulses of high-dose (>= 0.5 g/m2) or > 4 doses of low dose (500 mg every 2 weeks) or Average MMF > 2.5 g/day (or > 1800 mg/day of enteric coated mycophenolate sodium) for more than 8 weeks or Tacrolimus > 4 mg/day for more than 8 weeks; Cyclosporine for more than 8 weeks or during last 8 weeks prior to signing the ICF; Voclosporin for more than 8 weeks or during last 8 weeks prior to signing the ICF; Belimumab for more than 12 weeks or during last 12 weeks prior the ICF. 22. Receipt of any commercially available Janus kinase inhibitor or Bruton*s tyrosine kinase inhibitor <= 24 weeks prior to the ICF. 23. Participation in another clinical study with another intervention (besides anifrolumab) administered within 4 weeks prior to ICF signing or within 5 half-lives of the study intervention used in that study, whichever is longer 24. Lactating or pregnant females or females who intend to become pregnant or begin breastfeeding anytime from initiation of Screening through the Follow-up 12 weeks following last dose of study intervention and 6 weeks after the last dose of MMF (whichever is later).

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:	Pending
Start date (anticipated):	14-01-2022
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Anifrolumab

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-04-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-506359-68-00
EudraCT	EUCTR2021-002862-42-NL
CCMO	NL79120.056.21