A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis

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Main objective:To assess the efficacy of Orelvo (voclosporin) compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN)Secondary objective:To assess the safety and tolerability of Orelvo...

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

Summary

ID

NL-OMON49474

Source
ToetsingOnline

Brief title
AURORA 1: Aurinia Renal Response in Active Lupus with Voclosporin

Condition

- Autoimmune disorders

Synonym
Active Lupus Nephritis

Research involving

Human

Sponsors and support

Primary sponsor: Worldwide Clinical Trials
Source(s) of monetary or material Support: Aurinia Pharmaceuticals Inc.

Intervention

Keyword: Active, Lupus, nephritis

Outcome measures

Primary outcome

Renal response at Week 52 will be adjudicated by the Clinical Endpoints

Committee based on the following parameters:

* UPCR of *0.5 mg/mg, and

* eGFR *60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of

>20%, and

* Received no rescue medication for LN (see protocol Section 7.8, Prohibited

Therapy and Concomitant Treatment), and

* Did not receive more than 10 mg prednisone for *3 consecutive days or for *7

days in total during Weeks 44 through 52, just prior to the renal response

assessment.

Subjects who withdraw from the study prior to the Week 52 assessment will be

defined as non responders.

Secondary outcome

* Time to UPCR of *0.5 mg/mg

* Partial renal response as defined by 50% reduction from baseline in UPCR at

Weeks 24 and 52

* Time to 50% reduction in UPCR from baseline

* Renal response at Week 52 (based on definition of primary endpoint)

* Duration of UPCR <0.5 mg/mg

*Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each timepoint.

*Change from baseline in UPCR at each time point.

*Change from baseline in serum creatinine, urine protein, and eGFR.

*Change from screening in immunology parameters (complement 3 (C3), C4, and anti double-stranded DNA).

*Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of *2.5 mg between Weeks 16 to 24 and Weeks 44 to 52).

*Change from baseline in health-related quality of life at Weeks 12, 24, and 52.

*Health Resource Utilization at Weeks 24 and 52.

*Change from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity (SELENA-SLEDAI) Index score at Weeks 24 and 52.

Study description

Background summary

The trial AUR-VCS-2016-01 proposed indication is active lupus nephritis (LN).
LN is the most common serious manifestation of systemic lupus erythematosus (SLE). LN is divided into different classes according to the level of treatment required, using a classification system for renal biopsy pathology originally developed by the World Health Organization (WHO).
LN manifests as diverse patterns of immune complex-mediated renal disease

affecting glomerular, tubulointerstitial, and vascular compartments. It can lead to permanent and irreversible tissue damage within the kidney, resulting in end-stage renal disease (ESRD), and thus making LN a serious and potentially life-threatening condition.
The current treatment paradigm for LN includes two goals, based on the severity of disease. The first goal of treatment in subjects with active LN is intended to bring the disease under control as quickly as possible to limit the potential for extensive renal scarring or loss of life.
The second goal of treatment, after the patient successfully responds to treatment, is to maintain remission by preventing renal flares and any resulting deterioration in renal function. In this second phase of treatment, lower doses of both corticosteroids and immunosuppressant are used.
However, the treatment of SLE remains unsatisfactory. No therapy has been specifically approved for the treatment of LN in either the USA or Europe. In many patients, the disease is inadequately controlled, resulting in the progression to end-stage organ failure.
Current therapies, such as corticosteroids (CS) and other immunosuppressive drugs, which must be administered at high doses, can also lead to serious side effects.
In this trial, Investigational medicinal product Orelvo (voclosporin) is a Calcineurin inhibitor (CNI). CNIs are a class of immunosuppressants which reversibly inhibit immunocompetent lymphocytes, particularly T-lymphocytes in the G0 and G1 phase of the cell cycle, and also reversibly inhibit the production and release of lymphokines. CNIs mediates its suppressive effects by binding to an ubiquitous intracellular protein cyclophilin. This complex, in turn, inhibits the calcium- and calmodulin-dependent serine/threonine phosphatase activity of the enzyme calcineurin. Calcineurin inhibition then prevents the activation of various transcription factors necessary for the induction of cytokine genes during T-cell activation, such as interleukin-2, interleukin-4, tumor necrosis factor-*, granulocyte macrophage colony stimulating factor, and interferon-*.
Orelvo (voclosporin) is a next-generation CNI developed for the treatment of autoimmune diseases and for use in the prevention of organ graft rejection. Voclosporin is structurally similar to cyclosporine A (CsA) except for a modification of a functional group on the amino acid 1 residue of the molecule. This alteration has changed the binding of voclosporin to calcineurin leading to a 3- to 5-fold increase in potency when compared to CsA. This modification has also shifted metabolism away from amino acid 1, the major site of metabolism for CsA, thus altering the metabolic profile. This in turn has led to faster elimination of metabolites resulting in lower measured metabolite exposure as compared to CsA. The combination of increased potency and decreased measured metabolite exposure, for voclosporin as compared to CsA, has led to better pharmacokinetic (PK)/ pharmacodynamic predictability.
In the proposed AUR-VCS-2016-01 clinical study, it is planned to randomize approximately 324 subjects. One arm shall receive treatment with Orelvo softgel capsules containing 7.9 mg drug (23.7 mg twice daily (BID)) and the other arm shall receive matching placebo (162 subjects per arm). All subjects will

receive an initial treatment of intravenous (IV) methylprednisolone, followed by a reducing taper of oral corticosteroid. Additionally, all subjects will receive background therapy with mycophenolate mofetil (MMF).

Study objective

Main objective:
To assess the efficacy of Orelvo (voclosporin) compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN)

Secondary objective:To assess the safety and tolerability of Orelvo over 52 weeks compared with placebo in subjects with active LN

Study design

Prospective, randomized, placebo-controlled, double-blind, parallel-group, 52-week, international, multicenter, 2-arm comparison study of Orelvo versus matching placebo.

Intervention

NA

Study burden and risks

Because Orelvo is investigational, there is a risk of your lupus nephritis getting worse or not changing if the drug does not work for you. Signs of lupus activity will be closely monitored and patients will be managed according to medical practice if this occurs.
Use of immunosuppressants in general can increase risk of developing a serious infection which may lead to death, or may reduce body's ability to fight serious infections. Use of immunosuppressants in general can increase your risk of certain cancers.
Side effects reported by subjects and considered by the Study Doctor to be related to Orelvo treatment are described below.
Common side effects, those reported by >10% of subjects receiving Orelvo include high blood pressure and changes in kidney function. Less common side effects (>5% of subjects) include upper respiratory infections and headache. Other side effects reported by between 1 and 5% of subjects include sore joints, nausea, abdominal pain/discomfort, weakness, abnormal hair growth, and pain in your limbs extremities.
It is not known if you will experience any of these side effects. Since Orelvo is investigational, there may be other risks that are currently unknown or unforeseen. Any drug has the potential risk of an allergic reaction which, if serious and not treated promptly, can become life-threatening.

The side effects and discomforts reported for MMF include, but are not limited to mild to moderate stomach pain, nausea, vomiting, diarrhea, fever, anemia, headache, infection (including tuberculosis, opportunistic infections and Progressive Multifocal Leukoencephalopathy * a neurological disorder caused by a virus that can lead to brain damage), fluid retention, swelling, weakness, shakiness, pain, high blood pressure and a low amount of white blood cells. The most frequent side effects of corticosteroids are increased appetite, weight gain, high blood pressure, indigestion and nervousness or restlessness. There may also be side effects and discomforts from the treatments that are not yet known. In addition, when treated with intravenous (IV) methylprednisolone, you might experience some discomfort that includes bruising or infection at the IV site.
Some people have discomfort or pain when blood is collected. The insertion of needles into the arm can cause pain, swelling, bruising and occasionally fainting reactions; in rare occasions nerve damage can occur. Fainting reactions are usually harmless, of short duration, and typically produce feelings of weakness accompanied by sweating, slowing of the heart rate and an abnormal decrease in blood pressure. There is also a risk of infection and small blood clots in blood vessels.

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

Written informed consent before any study specific procedures are performed.
* Male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of screening (Visit 1).
* Previous diagnosis of SLE according to the American College of Rheumatology criteria
* Subjects with evidence of active nephritis, defined as follows:
- Kidney biopsy result within 2 years prior to screening indicating Class III, IV S, IV-G (alone or in combination with Class V), or Class V LN (see Appendix 3) with a doubling or greater increase of urine protein creatinine ratio (UPCR) within the last 6 months to a minimum of *1.5mg/mg for Class III/IV or to a minimum of *2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening must be reviewed with a medical monitor to confirm eligibility.
OR
- Kidney biopsy result within 6 months prior to screening indicating Class III, IV S or IV-G (alone or in combination with Class V) LN with a UPCR of *1.5 mg/mg at screening.
OR
- Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of *2 mg/mg at screening.
A biopsy can be performed during screening, if not available. The above criteria must be fulfilled at baseline.
* In the opinion of the Investigator, subject requires high-dose corticosteroids and immunosuppressive therapy.
* Subject is willing to take oral MMF for the duration of the study, either by continuing current MMF therapy or by initiating it on or before the Baseline Visit.
* Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception must be used
simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study

Exclusion criteria

1. Subjects unable or unwilling to give written informed consent and/or to comply with study procedures.
2. Estimated glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of *45 mL/minute/1.73 m2 at screening confirmed

before randomization.
3. Currently taking or known need for any of the medications listed in Section 7.8, Prohibited Therapy and Concomitant Treatment at screening or during the study. This includes prohibited medications prior to screening as specified in Section 7.8.1, Prohibited Medications.
4. Currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period.
5. A previous kidney transplant or planned transplant within study treatment period.
6. Any known hypersensitivity or contraindication to MMF, mycophenolic acid, cyclosporine, corticosteroids or any components of these drug products.
7. Current or medical history of:
* Congenital or acquired immunodeficiency.
* In the opinion of the Investigator, clinically significant drug or alcohol abuse within 2 years prior to screening.
* Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that is cervical intraepithelial neoplasia 1, but have been treated with conization or loop electrosurgical excision procedure and have had a normal repeat Papanicolaou test are allowed.
* Lymphoproliferative disease or previous total lymphoid irradiation.
* Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known HIV infection. Severe viral infection is defined as active disease requiring antiviral therapy.
* Active tuberculosis (TB), or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid (see Section 9.2.1, Screening Visit Procedures).
8. Other known clinically significant active medical conditions, such as:
* Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. QT interval duration corrected for heart rate using method of Fridericia exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening will result in exclusion.
* Liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin *2.5 times the upper limit of normal) at screening and, if abnormal at screening, then confirmed that the levels have returned to <2.5 times upper limit of normal before randomization.
* Chronic obstructive pulmonary disease or asthma requiring oral steroids.
* Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm3; absolute neutrophil count <1.3 × 103/*L; thrombocytopenia (platelet count <50,000/mm3).
* Active bleeding disorders.
* Current infection requiring IV antibiotics.
9. Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes (e.g., scleroderma with significant pulmonary hypertension; any condition for which additional immunosuppression is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes (e.g., Sjögren*s syndrome) are not excluded.
10. No vaccines using live organisms, virus or bacterial, are allowed during screening and while taking the study treatment.
11. Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening that may affect study conduct or interfere with study assessments or outcome.

12. Any other medical condition which, in the Investigator*s judgment, may be associated with increased risk to the subject or may interfere with study assessments or outcomes.
13. Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions.
14. Participation in another interventional clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to screening.
15. Subjects randomized and treated in a previous voclosporin clinical study.

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):	26-10-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orelvo
Generic name:	Voclosporin

Ethics review

Approved WMO Date:	20-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2017
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2019
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
EudraCT	EUCTR2016-004045-81-NL
ClinicalTrials.gov	NCT03021499
CCMO	NL60796.056.17

Study results

Date completed:	09-01-2019
Actual enrolment:	4