A Randomized, Controlled, Double-blind Continuation Study Comparing the Long*term Safety and Efficacy of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Subjects with Lupus Nephritis

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Primary Objective* To assess the long-term safety and tolerability of Orelvo compared with placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in subjects with LN. Secondary Objectives* To assess the...

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

Summary

ID

NL-OMON50319

Source
ToetsingOnline

Brief title
AURORA 2: Aurinia Renal Response in Lupus with Orelvo

Condition

- Autoimmune disorders

Synonym
Lupus Nephritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Lupus nephritis

Outcome measures

Primary outcome

*Adverse events (AE) profile and routine biochemical and hematological

assessments.

Secondary outcome

*Proportion of subjects in renal response defined as:

- UPCR of *0.5 mg/mg

- estimated glomerular filtration rate (eGFR) *60 mL/min/1.73 m2 or no

confirmed decrease from baseline in eGFR of >20%

-Received no rescue medication for LN

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

days in total during the 8 weeks prior to the renal response assessment.

*Subjects who withdraw from the study prior to the response assessment will be

defined as non-responders.

*Proportion of subjects in partial renal response defined as a 50% reduction

from baseline in UPCR.

*Renal flare as adjudicated by the Clinical Endpoints Committee (CEC).

*Extra-renal flare as adjudicated by the CEC.

*SELENA-SLEDAI scores by visit.

*Change in UPCR, eGFR, urine protein, and serum creatinine from AURORA 1 baseline.

*Change in immunology parameters (complement 3 (C3), complement 4 (C4), and anti double-stranded deoxyribonucleic acid (DNA)) from AURORA 1 baseline.

*Change in health-related quality of life (HRQoL) (SF-36) from AURORA 1 baseline.

*Healthcare Resource Utilization (HRU).

Study description

Background summary

The trial AUR-VCS-2016-02 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 AURORA 2 clinical study, subjects from the AURORA 1 study will have the option to be consented and enter this protocol. Subjects will continue to receive treatment as assigned by randomization in AURORA 1 (either Orelvo or matching placebo) plus background therapy of MMF and/or oral corticosteroids starting at the same dose as at the end of the AURORA 1 study. After 12 months treatment in the AURORA 2 Continuation Study (ie., 24 months of treatment in total), subjects with controlled urine protein creatinine ratio (UPCR) taking the 23.7 BID dose, will be permitted to reduce the dose of Orelvo to 15.8 mg BID, if considered appropriate and at the discretion of the Investigator.

Study objective

Primary Objective
* To assess the long-term safety and tolerability of Orelvo compared with placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in subjects with LN.
Secondary Objectives
* To assess the long-term efficacy of Orelvo compared with placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in subjects with LN.

Study design

Prospective, placebo-controlled, double-blind, parallel-group, 24-month continuation study to the AURORA 1 study (AUR VCS 2016 01).

Intervention

N/A

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

1. Written informed consent before any study-specific procedures are performed.
2. Male or female subjects who have completed 52 weeks of treatment with study drug in the AURORA 1 study. Subjects who had a temporary interruption and successfully restarted study drug during the AURORA 1 study will be allowed with Medical Monitor approval.
3. In the opinion of the Investigator, subject requires continued immunosuppressive therapy.
4. Women of childbearing potential must continue to use effective contraception

and have a negative urine pregnancy test at Month 12. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study (see Section5.4, Adequate/Effective Contraception).
5. Subject is willing to continue taking oral MMF for the duration of the study.

Exclusion criteria

1. Subjects unable or unwilling to give written informed consent and/or to comply with study procedures.
2. Currently taking or known need for any of the medications or food items listed in Section 7.8, Prohibited Therapy and Concomitant Treatment during the study.
3. Subjects currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period.
4. A planned kidney transplant within study treatment period.
5. Subjects with any 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.
6. Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions.
7. Vaccines using live organisms, virus or bacterial, while taking the study treatment.

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:	Completed
Start date (anticipated):	24-10-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-02-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2018
Application type:	First submission
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)
Approved WMO Date:	25-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2020
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	EUCTR2016-004046-28-NL
CCMO	NL64294.056.18

Study results

Date completed:	17-02-2021
Results posted:	21-03-2022
Actual enrolment:	3

First publication
09-03-2022