A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

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Primary• To evaluate the effect of ravulizumab on adjudicated On-Trial Relapses in adult patients with NMOSDSecondary• To evaluate the safety of ravulizumab in adult patients with NMOSD• To evaluate the effect of ravulizumab on adjudicated...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON49042

Source
ToetsingOnline

Brief title
Champion

Condition

- Autoimmune disorders
- Central nervous system infections and inflammations

Synonym
Neuromyelitis Optica Spectrum Disorder; disabling autoimmune inflammatory disorder of the central nervous system

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Efficacy, Neuromyelitis Optica Spectrum Disorder (NMOSD), Ravulizumab, Safety

Outcome measures

Primary outcome

• Time to first adjudicated On-Trial Relapse and relapse risk reduction

Secondary outcome

• Incidence of treatment-emergent adverse events (TEAEs), Treatment-emergent

serious adverse events (TESAEs), and TEAEs leading to study

drug discontinuation

• Adjudicated On-Trial ARR (analyzed relapse rate)

• Clinically important worsening in expanded disability status scale (EDSS)

• Change from baseline in EuroQoL-5D (EQ-5D)

• Clinically important change in Hauser ambulation index (HAI)

• Change in serum ravulizumab concentration over the study duration

• Change in serum free C5 concentration over the study duration

• Presence and titer of anti-drug antibodies (ADAs) over the study duration

Study description

Background summary

Neuromyelitis optica spectrum disorder is a severe disabling autoimmune inflammatory disorder of the CNS that predominately affects the optic nerves and spinal cord, and less commonly the brain. The disorder is ultra-rare, affecting 0.5 to 4.4 per 100,000 worldwide inhabitants (Pandit L, 2015).
The most common manifestations of NMOSD are characterized by recurrent, severe relapses of optic neuritis or transverse myelitis, which result in a stepwise accumulation of relapse-related neurologic disability that can be irreversible (Wingerchuk DM, 2006). The annualized relapse rate (ARR) for patients with NMOSD is estimated to be about 1 relapse per year per patient, with the vast majority of patients experiencing relapse (Flanagan EP, 2016; Ghezzi A, 2004; Jarius S, 2012).
In a study of AQP4-Ab positive neuromyelitis optica (NMO) patients, morbidity was significant with 18% experiencing permanent visual disability, 34% experiencing permanent motor disability, and 23% experiencing wheelchair dependency during the follow-up period (Kitley J, 2012)

SOLIRIS® (eculizumab), the first-in-class complement component C5 inhibitor, is the only therapy approved by the U.S. FDA for the treatment of NMOSD in adult patients who are anti-AQP4 Ab positive. Supportive treatments, including corticosteroids and other immunosuppressive therapies (ISTs), have been used based on clinical experience and consensus (Trebst C, 2014). Despite the use of ISTs as supportive therapy, a significant number of patients (> 50%) continued to experience disease relapses that resulted in incremental and permanent neurologic deficits and disability (Bichuetti DB, 2010; Jacob A, 2009).
Eculizumab has been demonstrated to be effective in reducing relapse risk. After the initial induction dose, eculizumab is administered every 2 weeks (q2w) to maintain adequate complement suppression. Neuromyelitis optica spectrum disorder is a chronic disease, and a frequent dosage regimen may impose a significant burden on patients, many of whom are disabled and require assistance with transportation.
Ravulizumab has a longer serum terminal elimination half-life and corresponding duration of pharmacologic activity relative to eculizumab. Ravulizumab was designed based on comprehensive modelling and simulation analyses to maintain efficacious concentrations across a longer dosing interval. The q8w dosage regimen is less burdensome for patients and has 4-fold fewer pharmacokinetic (PK) troughs, leading to fewer opportunities for achieving incomplete complement inhibition associated with sub-therapeutic exposure. The reduction in infusion frequency offers the potential to provide patients and physicians with an additional option for effective treatment of NMOSD while also improving quality of life (QoL) through fewer missed days of work, better treatment adherence, and improved accessibility.

Complement activation is a major determinant of disease pathogenesis in patients with NMOSD (Hinson SR, 2009; Nytrova P, 2014; Papadopoulos MC, 2012; Verkman, 2012). Binding of AQP4 IgG to the AQP4 water channel, which is highly expressed on astrocytic surfaces in the CNS, has been shown to lead to

hexameric assembly of immunoglobulin G (IgG). This in turn recruits and activates complement C1, the first step in activation of the complement cascade (Diebolder CA, 2014). Complement activation initiates an inflammatory cascade that induces permeabilization of the blood brain barrier and astrocyte necrosis. Lesions that form during this process are indicative of NMOSD and are positive for anti-AQP4 Abs and complement (Papadopoulos MC, 2012).
The therapeutic role of inhibition of terminal complement activation was demonstrated with eculizumab in Study ECU-NMO-301. Study ECU-NMO-301 was a randomized, double-blind, placebo-controlled, multicenter study that evaluated the safety and efficacy of eculizumab in patients with relapsing NMOSD. A significant effect on the time to first adjudicated On-trial Relapse was observed for eculizumab compared with placebo ($p<0.0001$). An approximately 94.2% reduction in the risk of relapse was observed in patients who received eculizumab compared with placebo (Pittock SJ, 2019). In conjunction with the efficacy results, the serum free C5 results indicated that immediate, complete, and sustained terminal complement inhibition was achieved.

Study objective

Primary
• To evaluate the effect of ravulizumab on adjudicated On-Trial Relapses in adult patients with NMOSD

Secondary
• To evaluate the safety of ravulizumab in adult patients with NMOSD
• To evaluate the effect of ravulizumab on adjudicated annualized relapse rate (ARR) in adult patients with NMOSD
• To evaluate the effect of ravulizumab on disease-related disability in adult patients with NMOSD
• To evaluate the effect of ravulizumab on quality of life (QoL) in adult patients with NMOSD
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD
• To characterize the pharmacokinetics (PK) of ravulizumab in adult patients with NMOSD
• To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with NMOSD
• To characterize the immunogenicity of ravulizumab in adult patients with NMOSD

Study design

Study ALXN1210-NMO-307 is a Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD.
Approximately 55 eligible adult patients with NMOSD will be enrolled.

This study will employ a single-arm treatment design, utilizing the placebo group from Study ECU-NMO-301 (conducted 2014 to 2018) as a contemporaneous external placebo control. This will allow for a robust assessment of ravulizumab as a treatment option for NMOSD.

There are 4 periods in this study: Screening Period, Primary Treatment Period, Long-Term Extension Period, and Safety Follow-up Period. Patients will be screened for eligibility for up to 6 weeks during the Screening Period. The Primary Treatment Period ends and the Long-Term Extension Period starts when the last patient completes the End of Primary Treatment (EOPT) Period Visit, which is initiated when all patients have completed the Week 26 Visit. All patients will continue to receive ravulizumab during the Long-Term Extension Period for up to 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. The total treatment duration for each patient will be up to 4 years. After the last dose of study drug or early discontinuation (ED), patients will be followed for 8 weeks.

This is a single-arm treatment study with no masking.

Intervention

Eligible patients will enroll into the study to receive intravenous infusions of ravulizumab.
The ravulizumab dose for each patient will be based on body weight.

The dosing regimen consists of a loading dose followed by maintenance dosing administered every 8 weeks (q8w).
The maintenance dosing should be initiated 2 weeks after the loading dose administration.

For each patient, the total duration of study participation will be up to 4 years and 14 weeks, including the Screening Period (up to 6 weeks), the Primary Treatment Period (between 26 weeks and 2 years), the Long-Term Extension Period (up to 2 years), and the Safety Follow-up Period (8 weeks).

Study burden and risks

Patients are asked to undergo procedures as described in the protocol table ' schedule of events', 1-4 on pages 16-24.
The study consists of a screening period up to 6 weeks, a primary treatment period of at least 26 weeks, a long-term extension period up to 2 years and a safety follow- up period of 8 weeks.
These procedures include:
- Physical exam, vital signs, demographic and medical history
- Ophthalmological exam

- Neurologic exam
- ECG
- OCT
- MRI
- Meningococcol vaccination
- Questionnaires: EQ-5D, SF-36, EDSS (including FSS)
- Blood and urine tests (including HIV)
- Optional blood test for DNA and RNA
- Optional Cerebrospinal fluid test for DNS and RNA
- Pregnancy tests in women of childbearing potential
- Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for 8 months following the last dose of the study drug.
- Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least 8 months following the last dose of study drug.

The study medication as well performing the study-related procedures, may cause discomforts and risks. Ravulizumab may also have discomforts and risks that are still unknown. These may be mild or serious and may be very serious, long-lasting, or may never go away. There is also a risk of death.

Following side effects have been reported based on the clinical experience in patients using Ravulizumab:
Meningococcal infection: patients receiving Ravulizumab, even after a single dose, are at increased risk for the development of serious infections caused by Neisseria meningitis. This is a bacterial infection that can hit the brain (menignococcal meningitsi) or be present in the blood (meningococcal sepsis). Meningococcal infections can rapidly become life-treating or fatal especially if not reorganized and treated early. Subjects will receive a vaccination against meningococcal infections. Vaccination alone may not be sufficient to prevent infection with Neissara meningitis.
Due to similar mechanism of action there is also a risk for the infection caused by the bacteria 'Neisseria gonorrhea' causing a gonococcal infection.

Side effects of Ravulizumab:
Very common side effects (seen in more than 10% of patients); diarrhea, nausea, vomitting, nasopharyngitis, headache.
Common side effects (seen in 1 to 10% of patients); abdominal pain, indigestion, flu-like illness, fever, chills, tiredness, muscle pain & spasm, back-pain, joint-pain, dizziness, rash & itchness.
Uncommon side effects (seen in less than 1% of patients); chills, upper respiratory tract infection (common cold)

There is a risk of a reaction occurring when receiving ravulizumab. Symptoms that may show that you are having a reaction include:
Headache, Lightheadedness, Itching, Muscle aches, Nausea, Vomiting, Sleepiness,

Skin redness, Abdominal discomfort, Excessive sweating
Tight feeling in chest, Fever, Chills or shivers, Shortness of breath, High or low blood pressure, Swelling of tissue (all or parts of your body), Hives Flushing, Rash, Heart palpitations (abnormal heart beat).

With any medication there is a risk of allergic reactions. Some symptoms of allergic reactions and/or anaphylaxis are:
Rash such as hives; may also include itching, Difficulty breathing, shortness of breath, tightness in the chest, and wheezing (noises while breathing) Dizziness or feeling faint, Tingling and swelling around the mouth, in your throat, or eyes, Fast pulse Very low blood pressure, Sweating, Seizures (convulsions), Loss of consciousness, Flushing or temporary reddening of the skin, (usually on the face), Possibly death.

Side effects and risks related to the study procedures:
• Blood draws
You may experience pain, bruising, or bleeding at the point where the blood was drawn. There is also the possibility of infection, but this is rare. Although the total amount of blood drawn over time is predicted to be well-tolerated, anemia (low levels of red blood cells) may occur.
• Intravenous (IV) infusions
An IV line is placed in your vein to administer the study drug. There may be discomfort during IV placement. Rarely, some people experience pain, bleeding, bruising, swelling, clotting of the vein, leakage of the IV fluid into their surrounding tissues, or infection at the location where the IV was placed. Meningococcal vaccination before start the study. If so, the vaccine will be injected into the arm. The vaccine can cause temporary swelling in the area where the vaccine was injected.
• ECG
The electrocardiogram is a painless procedure,it requires lying still in on examination table, which may be uncomfortable for some persons.
• MRI
MRI uses a large magnet to take images of the and spinal cord. An injection of a contrast dye (gadolinium) through a needle in the arm is given before the MRI scan. The main side effect associated with gadolinium, although rare, is an allergic reaction. The MRI scan does not hurt, but it requires the patient to be lying still for ca 45 minute to one hour.
• OCT
OCT is to examine the nerves in the back in the eyes. The procedure is painless. Eye drops prior to the procedure. These drops will cause light glare and make your vision blurry. These effects will go away after a few hours.
• Lumbar puncture
Lumbar puncture a procedure. A needle is inserted into the lower back and into the spinal canal, the fluid filled space around the spinal cord, to collect spinal fluid. Headache can occur following this procedure. Serious complications are extremely rare and include bleeding into the spinal canal, infection, injury to the spinal cord resulting in weakness and loss of

sensation or paralysis in the legs, spinal cord compression, and brain herniation.

Ravulizumab provides patients and physicians with an option for less frequent dosing, which allows greater access to care for those patients who may not initiate treatment on eculizumab, may discontinue eculizumab due to frequency of dosing, or who are currently receiving eculizumab every 2 weeks.

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

Participants are eligible to be included in the study only if all of the following criteria apply:
1. Patient must be 18 years of age or older, at the time of signing the

informed consent.
2. At least 1 attack or relapse in the last 12 months prior to the Screening Period
NOTE: Patients with a single life-time attack will be considered to satisfy inclusion criterion #3 if the attack occurred in the last 12 months.
3. Expanded Disability Status Scale (EDSS) score <= 7
4. Patients who enter the trial receiving supportive IST (eg, corticosteroids, azathioprine [AZA], mycophenolate mofetil [MMF], methotrexate [MTX], and tacrolimus [TAC]) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening with no plan to change the dose during the study period as follows:
a. If patients who enter the study are receiving AZA, they must have been on AZA for >= 6 months and have been on a stable dose for >= 2 months prior to Screening.
b. If patients who enter the study are receiving other ISTs (eg, MMF, MTX, or TAC), they must have been on the IST for >= 3 months and have been on a stable dose for >= 4 weeks prior to Screening.
c. If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for >= 4 weeks prior to Screening.
d. If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to Screening.
5. Vaccinated against N. meningitidis within 3 years prior to, or at the time of, initiating ravulizumab. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until 2 weeks after the vaccination.
Please see detailed list of inclusion criteria in the protocol

Exclusion criteria

Patients are excluded from the study if any of the following criteria apply:
1. History of N. meningitidis infection.
2. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
3. History of unexplained infections
4. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1
5. Previously or currently treated with a complement inhibitor.
6. Use of rituximab within 3 months prior to Screening
7. Use of mitoxantrone within 3 months prior to Screening
8. Use of Intravenous Immunoglobulin (IVIg) within 3 weeks prior to Screening
Prior/Concurrent Clinical Study Experience
9. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of Screening or 5 half-lives of the study drug, whichever is greater

Other Exclusions
10. Pregnant, breastfeeding, or intending to conceive during the course of the study
Please see detailed list of exclusion criteria in the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ravulizumab
Generic name:	ALXN1210

Ethics review

Approved WMO Date:	24-02-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-06-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2019-003352-37-NL
CCMO	NL71987.078.20

Study results

Summary results
Trial never started