A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER BASKET STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PATIENTS WITH ANTI*N METHYL D ASPARTIC ACID RECEPTOR (NMDAR) OR ANTI*LEUCINE RICH GLIOMA INACTIVATED 1 (LGI1) ENCEPHALITIS

Published: 06-07-2022
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This study has been transitioned to CTIS with ID 2023-504226-18-00 check the CTIS register for the current data. This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo in each of...

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

Summary

ID

NL-OMON51721

Source
ToetsingOnline

Brief title
WN43174 CIELO

Condition

- Autoimmune disorders
- Cranial nerve disorders (excl neoplasms)

Synonym
BRAIN Inflammation and encephalitis

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman - La Roche

Intervention

Keyword: autoimmune encephalitis, LGI1 encephalitis, NMDAR, Phase III, Satralizumab (RO5333787)

Outcome measures

Primary outcome

To evaluate the efficacy of satralizumab compared with placebo on degree of

disability and clinical severity:

• Proportion of participants with mRS score improvement = or > 1 from baseline

and no use of rescue therapy at Week 24

Secondary outcome

A. To evaluate the efficacy of satralizumab compared with placebo:

• Time to mRS score improvement = or > 1 from baseline without use of rescue

therapy

• Time to rescue therapy

• Time to seizure freedom (seizure freedom defined as a cessation of seizures

for at least 6 consecutive weeks) or cessation of status epilepticus without

use of rescue therapy

• Change in CASE score from baseline at Week 24

• MOCA total score at Week 24

• RAVLT score at Week 24 (LGI1 AIE cohort)

• mRS score at Week 24 (as measured on a 7-point scale; NMDAR AIE cohort)

B. To evaluate the safety of satralizumab compared with placebo:

• Incidence, seriousness, and severity of adverse events, with severity

determined according to National Cancer Institute Common Terminology Criteria

for Adverse Events, Version 5.0

• Change from baseline in targeted vital signs, clinical laboratory test

results, ECG results, weight, height (< 18 years only), and C-SSRS

Study description

Background summary

See chapter 22 for more background

Acute encephalitis is a rare and debilitating neurological disorder that develops in patients of all ages, presenting as a rapidly progressive encephalopathy as a consequence of brain inflammation (Venkatesan et al. 2013). Autoimmune encephalitis (AIE) includes disorders that are associated with an identifiable etiological driver, usually a tumor, and disorders that are regarded as idiopathic.

Although a majority of patients with cell surface antibodypositive disease achieve a stable condition with currently used treatment options, no prospective randomized trials have been reported to date in this population, and all therapeutics are used based on anecdotal evidence. Several limitations apply to the current AIE treatment paradigm that highlight remaining critical

unmet needs for treatments with rapid and demonstrated effects on long-term efficacy and safety. For example, not all patients respond to these medications, and deficiencies remain, including cognitive deficits, insufficient seizure resolution, dependence on high-dose corticosteroids, and a need for durable, faster-acting agents. There is an urgent need for prospectively generated evidence in AIE to guide treatment choice to address both acute as well as long-term effects of this rare neurological disorder.

Satralizumab is a recycling, humanized, antiIL-6 receptor (IL-6R) monoclonal antibody.

Given the pathological relevance of autoantibodies and pro-inflammatory T cells in AIE, IL-6 inhibition through satralizumab is expected to dampen immune mechanisms that underlie the clinical phenotype of AIE.

Study objective

This study has been transitioned to CTIS with ID 2023-504226-18-00 check the CTIS register for the current data.

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo in each of the following cohorts:
• NMDAR autoimmune encephalitis (AIE) cohort: adults and adolescents (12-16) with definite or probable NMDAR encephalitis
• LGI1 AIE cohort: adults with LGI1 encephalitis

Study design

This Phase III, randomized, double-blind, placebo-controlled, multicenter study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo for the treatment of NMDAR encephalitis and LGI1 encephalitis. For efficacy analyses, the NMDAR AIE and LGI1 AIE cohorts will be treated as separate populations in a basket study design. The study will include a screening period of up to 28 days in length, during which patients* eligibility will be evaluated for study participation. Screening will be followed by:
• Part 1: a primary treatment period of 52 weeks
• Part 2: an optional extension period lasting approximately 2 years from when the last participant enters the extension period or until commercial satralizumab is available for the treatment of AIE
A pharmacokinetic (PK) interim analysis will be performed once approximately 30 participants across both cohorts (to include approximately 15 participants receiving satralizumab) have received a minimum of 8 weeks of study treatment, to confirm that target concentrations are achieved.

The total duration of study participation for each individual is expected to be approximately 3 to 5 years.

Intervention

During Part 1, participants will be randomly assigned in a 1:1 ratio to receive placebo or 60 mg, 120 mg, or 180 mg depending of weight satralizumab in each of the NMDAR AIE and LGI1 AIE cohorts.

In Part 2, participants will be asked to choose from one of the following options:
• Option 1: continue on randomized, double blind study drug
• Option 2: start open label satralizumab based on body weight, as described above. In order to maintain the blinding of treatment assignment during Part 1, the following will occur:
-Participants who received placebo during Part 1 and choose to start open-label treatment in Part 2 will receive satralizumab SC at Weeks 0, 2, 4, and every 4 weeks (Q4W) thereafter.
-Participants who received satralizumab during Part 1 and choose to start open label treatment will continue to receive satralizumab SC Q4W in Part 2, with a dose of placebo administered at extension Week 2 in order to maintain the blinding of treatment assignment during Part 1.
• Option 3: stop study treatment and continue follow-up assessments

Study burden and risks

All currently available treatment options for AIE (including high dose corticosteroids and cyclophosphamide) carry substantial potential safety risks. There is no evidence from randomized controlled trials to support treatment decisions. In addition, not all patients respond to currently used medications, and deficiencies remain, including cognitive deficits, insufficient seizure resolution, dependence on high dose corticosteroids and a need for durable, faster acting agents. The proposed trial of satralizumab will address these unmet needs and establish the effectiveness of satralizumab in patients with NMDAR or LGI1 encephalitis. Taking into account the potential for efficacy in patients for which no approved drug exists, the safety profile for satralizumab, and the risk-mitigation measures for the study, the benefit/risk ratio is expected to be acceptable for satralizumab in the treatment of both NMDAR and LGI1 encephalitis.
Refer to Appendix 6 of the protocol for information on anticipated risks for satralizumab and risk mitigation measures, including guidelines for managing adverse events associated with satralizumab.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446AA
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446AA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

Zie paraaf 5.1. en 5.2 in het protocol V2
Inclusion Criteria for All Participants
* Capable of giving signed informed consent as described in Appendix 1
* Reasonable exclusion of tumor or malignancy before baseline visit (randomization)
* Onset of AIE symptoms, < 9 months before randomization
* Meet the definition of "New Onset" or "Incomplete Responder" AIE
- Has a stable (for at least 24 hours) mRS score = or > 2, measured at baseline
- Has received their first acute first-line therapy within 6 weeks prior to randomization (baseline visit)
- Has not received prior treatment with rituximab or any other ISTs

(e.g., cyclophosphamide, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, azathioprine) or tocilizumab for AIE

- Incomplete Responder: defined as a participant with NMDAR or LGI1 AIE who satisfies the following criteria:
o Has a stable (for at least 24 hours) mRS score = or > 2, measured at baseline
o Has received their first acute first-line therapy more than 6 weeks prior to randomization (baseline visit).
o Has received immunotherapy beyond their first acute first-line therapy course.

* For women of childbearing potential: agreement to remain abstinent or use adequate contraception during the treatment
period and for at least 3 months after the final dose of satralizumab or placebo

Additional Inclusion Criteria for the NMDAR AIE Cohort
In addition to the criteria outlined in Section 5.1.1, participants are eligible to be included
in the NMDAR AIE cohort only if all of the following criteria apply:
* Age, > 12 years at the time of signing Informed Consent Form
* Signed Assent Form
* Diagnosis of probable or definite NMDAR encephalitis

Additional Inclusion Criteria for the LGI1 AIE Cohort
In addition to the criteria outlined in Section 5.1.1, participants are eligible to be included
in the LGI1 AIE cohort only if all of the following criteria apply:
* Age, > 18 years at the time of signing Informed Consent Form
* Diagnosis of LGI1 encephalitis

Exclusion criteria

* Any untreated teratoma or thymoma at baseline visit (randomization). Teratoma or thymoma detected prior to or during the screening period is allowed if deemed cured after treatment (usually surgical removal) by 1 week prior to baseline
* History of carcinoma or malignancy, unless deemed cured by adequate treatment with no evidence of recurrence for = and > 5 years before screening (except basal cell and
squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that
have been completely excised and cured)
* For patients with NMDAR AIE, history of negative anti-NMDAR antibody in CSF using a cell based assay within 9 months of symptom onset

* Historically known positivity to an intracellular antigen with high cancer association
(e.g., anti-Hu, anti-Ma2, anti-CRMP5, anti-Yo, anti-amphiphysin, AMPA, mGluR5, and GABAB) or GAD-65
* Historically known positivity to any cell surface neuronal antibodies other than
NMDAR and LGI1 (e.g., caspr2, IgLON5, DPPX, GABAA, and neurexin-3α)
* Confirmed paraneoplastic encephalitis
* Confirmed central or peripheral nervous system demyelinating disease (e.g., multiple sclerosis, chronic inflammatory demyelinating polyneuropathy)
* Alternative causes of associated symptoms, including CNS infections, septic encephalopathy, metabolic encephalopathy, epileptic disorders, mitochondrial disease, Klein-Levin syndrome, Creutzfeldt-Jakob disease, rheumatologic disorders,
Reyes syndrome, or inborn errors of metabolism
* History of herpes simplex virus encephalitis in the previous 24 weeks
* Any previous/concurrent treatment with IL-6 inhibitory therapy (e.g., tocilizumab),
alemtuzumab, total body irradiation, or bone marrow transplantation
* Any previous treatment with anti-CD19 antibody, complement inhibitors, neonatal Fc
receptor antagonists, anti*B-lymphocyte stimulator monoclonal antibody (e.g., belimumab)
* Any previous treatment with T-cell depleting therapies, cladribine, or mitoxantrone
* Treatment with oral cyclophosphamide within 1 year prior to baseline
* Treatment with any investigational drug (including bortezomib) within 24 weeks prior
to screening (or within 5 half-lives of the investigational drug; whichever is longer)
* Concurrent use of more than one IST (e.g.. azathioprine, mycophenolate mofetil, or
IV cyclophosphamide) as background therapy
The combination of an OCS with another permitted IST drug is allowed.
* Contraindication to all of the following rescue treatments: rituximab, IVIG, high-dose
corticosteroids, or IV cyclophosphamide
* Any surgical procedure, except laparoscopic surgery or minor surgeries (defined as
procedures that require only local anesthesia or conscious sedation, i.e., do not
require general, neuraxial or regional anesthesia, and are done on an ambulatory/outpatient basis; e.g. toenail surgery, mole surgical excision, wisdom
tooth extraction), within 4 weeks prior to baseline, excluding surgery for thymoma or
teratoma removal

* Planned surgical procedure (except minor surgeries) during the study
* Evidence of progressive multifocal leukoencephalopathy
* Evidence of serious uncontrolled concomitant diseases that may preclude patient
participation, such as other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, and digestive system disease
* Congenital or acquired immunodeficiency, including HIV infection
* Active or presence of recurrent bacterial, viral, fungal, mycobacterial infection, or
other infection (excluding fungal infection of nail beds or dental caries) at baseline
* Infection requiring hospitalization or treatment with IV anti-infective agents within
4 weeks prior to baseline visit
* Positive hepatitis B (HBV) test at screening (defined as either of the following):
- Positive hepatitis B surface antigen (HBsAg)
- Positive total hepatitis B core antibody (total HBcAb) confirmed by a positive viral DNA polymerase chain reaction test
* Positive hepatitis C (HCV) test at screening (defined as positive HCV antibody and
detectable HCV RNA)
Participants with positive HCV antibody and undetectable HCV RNA 12 weeks after HCV treatment completion are eligible to participate in the study.
* Evidence of latent or active tuberculosis (TB) (excluding patients receiving chemoprophylaxis for latent TB infection)
If a patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration. Refer to Appendix 10 for details on TB screening and treatment.
* History of drug or alcohol abuse within 1 year prior to baseline
* History of diverticulitis or concurrent severe gastrointestinal (GI) disorders (such as
symptomatic diverticulosis) that, in the investigator*s opinion, may lead to increased
risk of complications such as GI perforation
* Receipt of live or live-attenuated vaccine within 6 weeks prior to baseline visit
* History of blood donation (1 unit or more), plasma donation or platelet donation
within 90 days prior to screening
* History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic
reactions)
* Active suicidal ideation within 6 months prior to screening, or history of suicide

attempt within 3 years prior to screening
* Any serious medical condition or abnormality in clinical laboratory tests that, in the
investigator's judgment, precludes safe participation in and completion of the study
* Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of study drug
Women of childbearing potential must have a negative serum pregnancy test result at screening and negative urine dipstick pregnancy test prior to initiation
of study treatment
* Certain laboratory abnormalities at screening (see protocol section 5.2: If a retest is conducted, the last value obtained determines the patient*s eligibility for
randomization.

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):	12-12-2022
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Satralizumab
Generic name:	Enspryng
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-07-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2024
Application type:	Amendment
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
EU-CTR	CTIS2023-504226-18-00
EudraCT	EUCTR2021-002395-39-NL
CCMO	NL80647.078.22