A Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pegcetacoplan in subjects with amyotrophic lateral sclerosis (ALS)

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The primary objective of this study is to assess the efficacy of twice per week subcutaneous (SC) doses of pegcetacoplan 1080 mg compared toplacebo in subjects with sporadic ALS as measured by the Combined Assessment of Function and Survival (CAFS)...

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

Summary

ID

NL-OMON54376

Source
ToetsingOnline

Brief title
MERIDIAN

Condition

- Neuromuscular disorders

Synonym
motor neurone disease (MND) or Lou Gehrig's disease

Research involving
Human

Sponsors and support

Primary sponsor: Apellis Pharmaceuticals, Inc
Source(s) of monetary or material Support: Apellis Pharmaceuticals;Inc.

Intervention

Keyword: Amyotrophic, Lateral, Sclerosis, study

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

• CAFS rank score (joint-rank score) at week 52

Primary Safety Endpoints:

• Incidence and severity of TEAEs

• Change from baseline in vital signs and clinical laboratory tests

• Positive responses (Yes) to the Columbia Suicide Severity Rating Scale

Secondary outcome

Secondary Efficacy Endpoints:

• Change from baseline in ALSFRS-R at week 52

• Change from baseline in %SVC (at clinic visits) at week 52

• Change from baseline in HHD megascore at week 52

• Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 52

• Time to death up to week 52

• Change from baseline in ALSAQ-40 at week 52

• Change from baseline of the randomized treatment period (visit 2) and of the

open-label treatment period (visit 15) to week 104 for ALSFRS-R, %SVC, HHD, and ALSAQ-40

• Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 104

• Time to death up to week 104

Exploratory Endpoints:

• Change from baseline in European Quality of Life-5 Dimensions-5 Level at week 52, week 104, and week 156

• Change from baseline in Zarit Burden Interview score at week 52, week 104, and week 156

• Change from baseline of %SVC (home spirometry) at week 52 and week 104

• Time to percutaneous endoscopic gastrostomy tube placement up to week 52, week 104, and week 156

• Change from baseline in serum neurofilament light chain at week 52, week 104, and week 156

• Change from baseline in serum phosphorylated neurofilament heavy chain at week 52,
week 104, and week 156

• Change from baseline in electrical impedance myography at week 52, week 104, and week 156 (only at select investigational sites chosen to complete this)

• Pegcetacoplan pharmacokinetic concentrations at week 52, week 104, and week 156

• Changes from baseline at week 52, week 104, and week 156 in complement

biomarkers:

* Classical hemolytic complement pathway activity

* Alternative hemolytic complement pathway activity

* C3 levels

• Immunogenicity: presence of antibodies to polyethylene glycol moiety and

peptide

moiety of pegcetacoplan during the randomized and open-label treatment periods

• Change from baseline of the randomized treatment period (week 1) and of the

open-label treatment period (week 52) to week 156 for ALSFRS-R, %SVC

(in-clinic),

HHD, and ALSAQ-40

• Time to death, permanent tracheostomy, or permanent assisted ventilation up to

week 156

• Time to death up to week 156

Study description

Background summary

The proposed trial is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pegcetacoplan (also known as APL-2) in subjects with Amyotrophic Lateral Sclerosis (ALS). ALS is a fatal neurodegenerative disorder for which there is no cure and limited treatment options. Therefore, there is a need to investigate therapies that could potentially improve function and increase survival in this patient population.
Pegcetacoplan is a PEGylated peptide wherein pharmacologically active pentadecapeptide is chemically bound to each end of a linear polyethylene glycol (PEG) with average molecular weight of 40 kDa (PEG40). The peptide moieties bind to primate complement C3 and exert a broad inhibition of the complement cascade. The PEG40 portion of the drug molecule imparts improved

solubility and longer residence time in the body after administration of the drug. Subcutaneously administered pegcetacoplan is being studied in multiple other complement-mediated indications (paroxysmal nocturnal hemoglobinuria [PNH], cold agglutinin disease [CAD], and complement-dependent nephropathies). To date, no safety signals have emerged from ongoing studies that preclude further development of pegcetacoplan. Clinical data from completed studies in other indications suggest that targeting C3 may be an effective therapeutic approach. Based on its mechanism of action, pegcetacoplan has the potential to slow the progression of ALS by targeting the complement system at the level of C3 thus preventing the degeneration of motor neurons.
In this study, pegcetacoplan will be administered as a SC infusion at a dose of 1080 mg twice per week using a commercially approved pump. A dose of 1080 mg twice per week was associated with substantial and sustained inhibition of the complement system and was well-tolerated in both healthy volunteers and patients with other complement-mediated diseases. Therefore, a dose of 1080 mg twice per week is planned as the most appropriate regimen for this clinical trial, maximizing potential pharmacology and benefit to the patients.
Drug/device compatibility testing has been conducted and demonstrated that pegcetacoplan is compatible with the delivery devices that will be used within the study. Additional details are provided in the IMPD.
Study APL2-ALS-206 has been designed in accordance with the EMA Guideline on clinical investigations of medicinal products for the treatment of amyotrophic lateral sclerosis, November 2015. As such, the use of placebo in this trial is appropriate in order to assess the effects of pegcetacoplan on ALS. Patients enrolled in the study will be allowed to use riluzole or edaravone (in countries where it is approved) during the study if the dose remains stable throughout the duration of study participation.
Approximately 228 subjects will participate in this study at up to 70 research sites globally, for a duration of 116 weeks. After a 6 week screening period, subjects will be randomized in a 2:1 ratio to either the pegcetacoplan treatment arm or the placebo arm. Safety and efficacy will be assessed and will include once per week at-home measurements, monthly calls, and clinic visits. All subjects completing 52 weeks of randomized treatment will be treated with open label pegcetacoplan 1080 mg twice per week up to Week 104 followed by an exit visit 6 weeks later unless they enter the Sponsor-planned long-term extension protocol. Subjects who do not continue to open label treatment will continue to an exit visit 6 weeks after the last dose.

Study objective

The primary objective of this study is to assess the efficacy of twice per week subcutaneous (SC) doses of pegcetacoplan 1080 mg compared to placebo in subjects with sporadic ALS as measured by the Combined Assessment of Function and Survival (CAFS) rank score (joint-rank score).

Secondary objectives:

•To assess the effect of pegcetacoplan compared to placebo as measured by the Revised ALSFRS-R score
•To assess the effect of pegcetacoplan compared to placebo on disease progression as measured by respiratory function through percentage of slow vital capacity (%SVC)
•To determine the effect of pegcetacoplan compared to placebo on muscle strength as measured by handheld dynamometry (HHD)
•To determine the effect of pegcetacoplan compared to placebo on survival or specified state of disease progression
•To assess the effect of pegcetacoplan compared to placebo on healthrelated quality of life as measured by ALSAQ-40
•To assess the safety of pegcetacoplan during the randomized and openlabel treatment periods through incidence and severity of TEAEs, clinical laboratory tests (hematology, chemistry), vital signs, and physical examinations
•To assess the long-term efficacy of pegcetacoplan using ALSFRS-R, %SVC,HHD, and ALSAQ-40 during the open-label treatment period

Study design

This is a phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study
of SC pegcetacoplan 1080 mg twice per week conducted in approximately 228 subjects with ALS.
The planned length of participation in the study for each subject is a maximum of approximately
168 weeks. This study will consist of 5 parts:
• Part 1: Up to 6-week screening period
• Part 2: 52-week randomized treatment period
• Part 3: 52-week open-label (pegcetacoplan) treatment period
• Part 4: 52-week open-label long-term extension treatment period
• Part 5: 6-week off-treatment follow-up period

Part 1
Screening (Up to 6 Weeks)
• Informed consent will be obtained at screening prior to any study-related procedures being
conducted
• Subjects (and/or caregiver) will be trained on the use of at-home assessments.

Part 2
Randomized Treatment Period (52 Weeks)
• Approximately 228 subjects who meet all of the inclusion criteria and none of the
exclusion criteria will be randomized 2:1 to either the pegcetacoplan treatment group or to
the placebo treatment group. Safety and efficacy will be assessed and will

include once per
week at-home measurements, monthly calls, and clinic visits.
• Pegcetacoplan treatment group
* Subjects randomized to pegcetacoplan will receive SC pegcetacoplan 1080 mg twice
per week for 52 weeks.
• Placebo treatment group
* Subjects randomized to placebo will receive SC placebo twice per week for 52 weeks.
Subjects who discontinue treatment early and do not complete Part 2 will continue to Part 5.

Part 3
Open-Label (Pegcetacoplan) Treatment Period (52 weeks)
At the end of Part 2, all subjects from both treatment groups will continue to Part 3. All subjects
participating in Part 3 will be treated with pegcetacoplan 1080 mg twice per week up to week 104.
Subjects who complete Part 3 will enter Part 4. Subjects who do not continue to Part 3, or who have
started Part 3 but discontinue treatment early, will continue to Part 5.

Part 4
Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period (52 weeks)
At the end of Part 3, any subject who, in the opinion of the investigator, is experiencing clinical benefit
from pegcetacoplan administration will be invited to continue to Part 4, the open-label long-term
extension treatment period. All subjects participating in Part 4 will be treated with pegcetacoplan
1080 mg twice per week up to week 156. Subjects who complete Part 4 will enter Part 5. Subjects who
do not continue to Part 4, or who have started Part 4 but discontinue treatment early, will continue to
Part 5.

Part 5
Off-Treatment Follow-up Period (6 weeks)
During Part 5, all subjects who have discontinued the investigational product (blinded
pegcetacoplan/placebo or open-label pegcetacoplan) will complete a follow-up visit 6 weeks later.

Intervention

In this study, pegcetacoplan will be administered as a SC infusion at a dose of 1080 mg twice per week using a commercially approved pump. A dose of 1080 mg

twice per week was associated with substantial and sustained inhibition of the complement system and was well-tolerated in both healthy volunteers and patients with other complement-mediated diseases. Therefore, a dose of 1080 mg twice per week is planned as the most appropriate regimen for this clinical trial, maximizing potential pharmacology and benefit to the patients. Drug/device compatibility testing has been conducted and demonstrated that pegcetacoplan is compatible with the delivery devices that will be used within the study. Additional details are provided in the IMPD.

Approximately 228 subjects will participate in this study at up to 70 research sites globally, for a duration of 116 weeks. After a 6 week screening period, subjects will be randomized in a 2:1 ratio to either the pegcetacoplan treatment arm or the placebo arm. Safety and efficacy will be assessed and will include once per week at-home measurements, monthly calls, and clinic visits. All subjects completing 52 weeks of randomized treatment will be treated with open label pegcetacoplan 1080 mg twice per week up to Week 104 followed by an exit visit 6 weeks later unless they enter the Sponsor-planned long-term extension protocol. Subjects who do not continue to open label treatment will continue to an exit visit 6 weeks after the last dose.

Study burden and risks

Risks with pegcetacoplan:
• Injection site reaction: redness, itching, pain, swelling, hardening
• Tiredness
• Dizziness
• Headache
• Restlessness
• Fever
• Severe infection
• Rash
• Urticaria
• Allergic reaction
• Diarrhea
• Flatulence
• Nausea
• Calcium increased
• Liver enzymes increased
• Decrease of red blood cells
• Decrease of blood platelets

Risks with placebo: mild injection/infusion site reactions.

Blood Draws: tenderness, pain, bruising, bleeding and/or infection.

ECG:minor skin irritation from the electrodes.

Pregnancy risks: There is limited data about the possible risk of pegcetacoplan to pregnant women and the unborn baby. Therefore, pegcetacoplan should not be given to pregnant women and women who are breastfeeding.

Contacts

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US
Scientific
Apellis Pharmaceuticals, Inc

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Waltham MA 02451
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Sporadic ALS diagnosed as definite, probable, or laboratory-supported probable as defined
by the revised El Escorial criteria (Brooks et al. 2000)
2. At least 18 years of age
3. Slow vital capacity >=60% of the predicted value at screening
4. Onset of ALS symptoms within 72 weeks prior to screening
5. Total ALSFRS-R score of >=30 at screening

6. Women of childbearing potential defined as any woman who has experienced menarche
and who is NOT permanently sterile or postmenopausal
a. must have a negative pregnancy test at screening and
b. must agree to use protocol defined methods of contraception for the duration of the
study and 90 days after their last dose of investigational product.
i. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.
7. Males must agree to
a. use protocol defined methods of contraception and
b. refrain from donating sperm for the duration of the study and 90 days after their
last dose of investigational product.
8. Have vaccination against Streptococcus pneumoniae, Neisseria meningitidis (types A, C,
W, Y, and B), and Haemophilus influenzae (type B) either within 5 years prior to baseline
visit 2b, or agree to receive vaccination at least 7 days prior to baseline visit 2b.
Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within
acceptable local limits).
9. Willing and able to give informed consent and comply with study procedure and
assessments (including at-home assessments

Exclusion criteria

Confirmed or suspected other causes of neuromuscular weakness
2. Diagnosis of another neurodegenerative disease(s)
3. Subject with significant cognitive impairment, clinical dementia, or psychiatric illness that
in the opinion of the investigator may increase subject*s risk by participating in the study
or confound the outcome of the study
4. Subjects with a significant pulmonary disorder not attributed to ALS or who require
treatments that might complicate the evaluation of the effect of ALS on respiratory
function (eg, chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis,
pulmonary arterial hypertension)
5. Current use or anticipated need, in the opinion of the investigator, of a

diaphragm pacing
system during the randomized treatment period
6. Riluzole initiation or change in dose within 30 days prior to the start of the screening
period or planned initiation during study participation. If using riluzole, the subject should
remain on the drug throughout Part 2 of study participation, but the dosage may be altered
or the drug discontinued at any time by the investigator for any safety concern.
Riluzole-naïve subjects are allowed in the study.
7. Edaravone initiation or change in dose within 60 days prior to the start of the screening
period or planned initiation during study participation. If using edaravone, the subject
should remain on the drug throughout Part 2 of study participation, but the dosage may be
altered or the drug discontinued at any time by the investigator for any safety concern.
Edaravone-naïve subjects are allowed in the study.
8. Positive response to Item 4 or 5 of the Columbia Suicide Severity Rating Scale
9. Subjects with detectable hepatitis C by polymerase chain reaction at screening
10. Subjects with chronic inactive hepatitis B with viral loads >1000 IU/mL (>5000
copies/mL) at screening. Eligible subjects who are chronic active carriers (<=1000 IU/mL)
must receive prophylactic antiviral treatment according to local country guidelines
(eg, entecavir, tenofovir, lamivudine)
11. History of an aggressive lymphoma or presence of a lymphoma requiring therapy by itself
12. Active or overt malignant disease other than basal cell carcinoma or cutaneous squamous
cell carcinoma
13. Received organ transplant
14. Presence or suspicion of liver dysfunction as indicated by elevated alanine aminotransferase,
aspartate aminotransferase, or bilirubin levels >2 × the upper limit of normal
15. Presence or suspicion of severe recurrent or chronic infections that, in the opinion of the
investigator, increase the subject*s risk by participating in the study.
16. Participation in any other investigational drug trial or exposure to other investigational
agent, device, or procedure within 30 days or within 5-half lives of the treatment

(whichever is longer) prior to the start of the screening period or during study participation
17. Use of any other complement inhibitor within 30 days or within 5-half lives of the treatment
(whichever is longer) prior to the start of the screening period or during study participation
18. If breastfeeding, unwilling to discontinue for the duration of the study and for at least
6 months after final dose of drug
19. Inability to cooperate or any condition that, in the opinion of the investigator, could increase
the subject*s risk by participating in the study or confound the outcome of the study
20. Subjects with known allergy or hypersensitivity to pegcetacoplan or to any of the components
21. Known or suspected hereditary fructose intolerance

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-12-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Pegcetacoplan
Generic name:	NA

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-07-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	10-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2019-003797-10-NL
ClinicalTrials.gov	NCT04579666
CCMO	NL74696.041.20

Study results

Date completed:	22-06-2023
Actual enrolment:	5

Summary results
Trial ended prematurely