A Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene

Published: 03-03-2020
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This study has been transitioned to CTIS with ID 2023-506873-36-00 check the CTIS register for the current data. The primary objective of this study is: Part 1: To evaluate the efficacy of AL001 compared with placebo as measured by CDR® plus NACC...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON52667

Source
ToetsingOnline

Brief title
AL001-3

Condition

- Dementia and amnestic conditions

Synonym
a brain disorder that affects behavior, causing difficulty in planning activities, communicating

with others, Frontotemporal dementia (FTD), language cognition, or movement, or performing everyday tasks.

Research involving
Human

Sponsors and support

Primary sponsor: Alector Inc
Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Frontotemporal Dementia, FTD, Phase 3, progranulin gene mutation

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

• The CDR® plus NACC FTLD-SB

Secondary outcome

Secondary Endpoints

• Clinical Global Impression Severity (CGI S)

• Clinical Global Impression Improvement (CGI I) score

• The changes from baseline in the scores of the following COAs:

o Frontotemporal Dementia Rating Scale (FRS)

o Repeatable Battery for the Assessment of Neuropsychological

Status (RBANS)

Secondary PD Endpoints:

• The changes from baseline in the following:

o Structural volumetric magnetic resonance imaging (MRI) whole

and regional brain volume

o Progranulin protein (PGRN) concentrations in plasma and

optional cerebrospinal fluid (CSF)

o Neurofilament light chain (NfL) concentrations in serum and

optional CSF

Secondary Safety Endpoints:

• Incidence, nature, and severity of adverse events and serious adverse events

• Physical examination abnormalities

• Neurological examination abnormalities

• Changes in vital signs from baseline over time

• Changes in electrocardiograms from baseline over time

• MRI abnormalities

• Changes in clinical laboratory tests from baseline over time

• Sheehan-Suicidality Tracking Scale (Sheehan STS)

• Incidence of ADAs to AL001

Study description

Background summary

Frontotemporal dementia is a rare progressive disease that affects behavior, language cognition, or movement, causing difficulty in planning activities, communicating with others, or performing everyday tasks. The disorder is identified by the presenting signs and symptoms such as behaving inappropriately at work or in social settings, difficulty speaking and understanding language, or problems with movement or daily activities. There are no approved therapies to slow or halt the disease. However, the symptoms of FTD may be managed with medications by the treating physician. The length of

progression of the disease may vary from 2 to 20 years once properly diagnosed and may depend on the underlying cause of FTD. Some individuals have a family history of FTD (familial or hereditary FTD) caused by a gene mutation that affects the proteins essential for normal brain cell functioning and survival. Mutations in the progranulin gene reduce the levels of progranulin in the body. Progranulin is a protein involved in cell survival and regulating inflammation. Normal levels of progranulin are required for the brain to work properly.
AL001 is being tested for the treatment of individuals who have a progranulin gene mutation that causes FTD.
AL001 is an antibody, a molecule that can bind to other molecules or receptors. AL001 attaches to a receptor called Sortilin, blocking the destruction of the progranulin protein, leading to higher levels of progranulin in the body.

Study objective

This study has been transitioned to CTIS with ID 2023-506873-36-00 check the CTIS register for the current data.

The primary objective of this study is:
Part 1: To evaluate the efficacy of AL001 compared with placebo as measured by CDR® plus NACC FTLD-SB.
Part 2: To assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of double-blinded treatment on Part 1 of the study

Secondary Efficacy:
To evaluate the efficacy of AL001 compared with placebo as measured by CGI-S.
To evaluate the efficacy of AL001 compared with placebo as measured by CGI-I
To evaluate the efficacy of AL001 compared with placebo as measured by RBANS
Pharmacodynamic: To evaluate the Pharmacodynamic (PD) of AL001 compared with placebo as measured by disease pathology biomarkers
Safety Objective: To evaluate the safety and tolerability of AL001 compared with placebo as measured by safety assessments and ADAs

Study design

This is a multicenter Phase 3, randomized, double blind, placebo controlled, Bayesian adaptive study to evaluate the efficacy and safety of AL001 compared to placebo in participants who are carriers of heterozygous loss of function GRN mutations causative of FTD.

Up to approximately 180 participants will be randomly assigned, in a double blind fashion, to receive AL001 or placebo in a 2:1 ratio (AL001:placebo).

Part 1 of the study will include a screening period (within 6 weeks prior to

randomization), a treatment period and an 8 week safety follow up period concluding with the Study Completion Visit. Upon completion of the double blind study treatment period, participants who qualify are planned to be offered an OLE study with AL001 (to be described in a separate protocol.

Part 2 is an optional 96-week OLE period for eligible participants who have completed Part 1.

Intervention

The study has two parts: A treatment period Part 1 (in total max. 96 weeks), followed by an open-label extension (OLE) period Part 2 (in total max. 96 weeks) for eligible participants who have completed Part 1.

Study burden and risks

In another study, a total of 64 participants were enrolled. Of the 64 participants enrolled in the Phase 1 study, the most common discomforts reported are: headache, headache after lumbar puncture, vomiting, lipase increase (measure of an inflamed or injured pancreas), anaemia (low red blood cell count), myalgia (muscle pain) and upper respiratory tract infection (infection of the nasal passages or sinuses) For those who have decided to participate in the optional lumbar puncture assessment, the potential side effects are post lumbar puncture syndrome (e.g., headache after lumbar puncture) and puncture site pain.

The side effects that were reported to be related to AL001 included: Post-lumbar puncture syndrome (headache after lumbar puncture procedure), Myalgia (muscle pain), Lipase increase (measure of an inflamed or injured pancreas), Tachycardia (fast heartbeat), Murphy*s sign positive (physical examination finding suggesting an inflamed gallbladder).

• Risk of developing Antidrug antibody (ADA): There is a chance that his/her body will develop antibodies against AL001 or that a hypersensitivity reaction (which can be severe and life threatening) will be induced. Theoretically this means that if you should need AL001 as therapy in the future, your response to treatment by this drug may be reduced or absent, and/or you may get a hypersensitivity reaction. Of the Phase 1 participants, 16 showed positive results for anti-drug antibodies. The impact of anti-drug antibodies on safety or efficacy of AL001 is still unknown.
• Infusion Risks: Infection may occur causing redness and discharge at the site with an elevated temperature. Infusion-related reactions include allergic reactions reactions, which can be severe and life threatening. These reactions are experienced by patients during the infusion of monoclonal antibody therapy and/or within hours of an infusion. Symptoms can include flushing, difficulty breathing, breathlessness (tightening of the muscles), reddening of the face,

changes in heart rate and blood pressure, sudden feeling of tightening thorax (in the walls of your lungs), back pain, fever, hives, swelling, nausea, and all types of rashes.
• Allergic Reactions: Allergic reactions can occur with any drug and this can be in the form of itching, difficulty breathing, and a skin rash and/or drop in blood pressure.
• Drawing blood may be painful or cause some bruising.

Contacts

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Scientific
Alector Inc

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Key Inclusion Criteria:
Part 1
• Known carrier progranulin genetic mutation causing FTD.

• CDR® plus NACC-FTLD score 0-2.
• If symptomatic, one of the criteria for the diagnosis of probable behavioral variant FTD or FTD-semantic subtype or FTD-Progressive Nonfluent Aphasia.
• Study partner who consents to study participation and who cares for/visits the patient daily for at least 5 hours per week.
• Written informed consent must be obtained and documented (from the patient or, where jurisdictions allow it, from their legal decision maker).

Part 2: Participant must complete Part1:
• Participant is willing and able to give informed consent to continue treatment with AL001. If the study participant is not competent, a legally authorized representative must provide informed consent on his or her behalf.
• Is willing and has the ability to comply with OLE requirements, in the opinion of the investigator.
• Has availability of a person ("study partner") who can continue to assist with assessments throughout the OLE evaluation period. (For more information please refer to the protocol or as described on PART 1, inclusion criteria number 8).

Exclusion criteria

Part 1
• Dementia due to a condition other than FTD including, but not limited to, Alzheimer's disease, Parkinson's disease, Parkinsonism, REM behavior disorder, dementia with Lewy bodies, Huntington disease, or vascular dementia.
• Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
• Current uncontrolled hypertension, diabetes mellitus or thyroid disease.
• Clinically significant heart disease, liver disease or kidney disease.
• History or evidence of clinically significant brain disease other than FTD.
• Females who are pregnant or breastfeeding, or planning to conceive within the study period.
• Any experimental vaccine or gene therapy.
• History of cancer within the last 5 years with the exception of basal cell or squamous cell carcinoma.
• Current use of anticoagulant medications (e.g., coumadin, heparinoids, apixaban).
• Residence in a skilled nursing facility, convalescent home, or long term care facility at screening; or requires continuous nursing care.

Part 2
Part 1 participants are not eligible for continued treatment with AL001 OLE if any of the following apply:
• Part 1 participant has been admitted to a skilled nursing facility,

convalescent home, or long-term care facility at screening and requires continuous nursing care (i.e., >3 months).
• Part 1 participant has a medical condition or extenuating circumstance that, in the opinion of the investigator, continued treatment with AL001 at the conclusion of Part 1 is not beneficial or safe for the participant.

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:	Recruiting
Start date (anticipated):	24-11-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AL001
Generic name:	AL001

Ethics review

Approved WMO

Date:	03-03-2020
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2021
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2022
Application type:	Amendment
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Approved WMO Date:	28-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Approved WMO Date:	20-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2024
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	CTIS2023-506873-36-00
EudraCT	EUCTR2019-004066-18-NL
ClinicalTrials.gov	NCT04374136
CCMO	NL72487.078.20