A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of Granulin or C9orf72 Mutations Causative of Frontotemporal Dementia

Published: 06-06-2019
Last updated: 14-03-2025

Primary ObjectivePart1: To evaluate the safety and tolerability of intravenous (IV) administration of AL001 over up to 96 weeks in asymptomatic and symptomatic carriersof a granulin (GRN) mutation causative of frontotemporal dementia (FTD) and in...

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

Summary

ID

NL-OMON52800

Source
ToetsingOnline

Brief title
An Open-Label Study to Evaluate Safety of long-term AL001 dosing in FTD

Condition

- Dementia and amnestic conditions

Synonym
a brain disorder which involves dying of nerve cells in the front and sleeping lobes,

Frontotemporal dementia (FTD)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AL001-2, Frontotemporal Dementia, FTD, Phase 2

Outcome measures

Primary outcome

Primary Safety Endpoints:

To assess the potential effect of cumulative exposure on the safety profile of

AL001, the following will be evaluated by dose, such as by using tertiles of

the actual dose (normalized to weight) received:

• Incidence, nature, and severity of AEs and SAEs

• Incidence of treatment discontinuations and study discontinuations due to AEs

• Physical examination abnormalities

• Neurological examination abnormalities

• Changes in vital signs from baseline over time

• Changes in ECGs from baseline over time

• MRI abnormalities after dosing relative to baseline

• Changes in clinical laboratory tests from baseline over time

• Sheehan Suicidality Tracking Scale (Sheehan-STS)

• Incidence of ADAs to AL001

Secondary outcome

Secondary PK Endpoints:

• Serum concentration of AL001 at specified timepoints

• AL001 PK parameters (if data permit)

o Cmax

o Ctrough

o AUCss

Secondary PD Biomarker Endpoints:

• The overall change from baseline in PGRN in CSF

• The overall change from baseline in PGRN in plasma

Study description

Background summary

Frontotemporal dementia (FTD) is the second most common early-onset form of dementia after Alzheimer*s disease, afflicting approximately 60,000 Americans (Tatton 2014) and 113,000 people in the European Union, Norway, Iceland, and Liechtenstein combined (EMA 2016).
Frontotemporal dementia is typified by prominent executive dysfunction, behavioral and personality changes, and language deficits. A family history is present in approximately 40% of FTD cases, with about 10% showing an autosomal dominant pattern of inheritance, indicating a strong genetic component.

Granulin (GRN) mutations account for up to 20% of all heritable FTD cases, and 5 to 10% of all cases of FTD are caused by a loss-of-function mutation in 1 allele of GRN. Heterozygous GRN deficiency almost invariably leads to development of FTD, making GRN a causal gene for the disease.
C9orf72 hexanucleotide repeat expansions are also a significant contributor to FTD pathology. Expansion of a non-coding hexanucleotide repeat in C9orf72 is the most common single cause of FTD, representing approximately 25% of familial cases and 6% of sporadic FTD cases.

FTD patients with GRN and C9orf72 mutations exhibit a common pathology in frontotemporal degeneration associated with TDP-43 protein-related

accumulation.Therapeutics targeted at reducing TDP-43 pathology and restoring lysosomal function may thus
also slow FTD disease progression in patients with either GRN or C9orf72 mutations.

Given the marked behavioral and personality changes of FTD and early onset of the disease, FTD patient care represents a significant burden for caregivers, families, and society.

Study objective

Primary Objective
Part1: To evaluate the safety and tolerability of intravenous (IV) administration of AL001 over up to 96 weeks in asymptomatic and symptomatic carriers
of a granulin (GRN) mutation causative of frontotemporal dementia (FTD) and in symptomatic carriers of a C9orf72 mutation causative of FTD.
Part2: The primary objective of the optional OLE period of the study is to assess the long-term safety and tolerability of IV administration of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study.

Secondary Objectives
Part1: The secondary objectives of this study are to evaluate the effect of IV administration of AL001 over up to 96 weeks in asymptomatic and symptomatic carriers of a GRN mutation causative of FTD and in symptomatic carriers of a C9orf72 mutation causative of FTD on the
following:
• Pharmacokinetics (PK)
Longitudinal plasma and CSF PGRN concentration levels
•Longitudinal levels of Sortilin in WBCs

Part 2: to assess the long-term effect of IV administration of AL001 in participants who have completed 96 weeks of treatment on Part 1 on the following:
• Pharmacokinetics
• Longitudinal plasma progranulin concentration levels
• Longitudinal blood and plasma levels of exploratory pharmacodynamic biomarkers of neurodegeneration, lysosomal function, and glial activity
• MRI measures to evaluate changes in the brain; Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical
outcome assessments (COAs)• Clinical progression as measured by COAs

Exploratory Objectives
The exploratory objectives of this study are to assess the effect of IV administration of AL001 over up to 96 weeks in asymptomatic and symptomatic carriers of a GRN mutation causative of FTD and in symptomatic carriers of a

C9orf72 mutation causative of FTD on the following:
• Longitudinal blood, plasma, and CSF concentration levels of exploratory pharmacodynamic (PD) biomarkers of neurodegeneration, lysosomal function, and microglial activity
in the brain
• Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical outcome assessments (COAs)
• Clinical progression as measured by COAs

Study design

This is a Phase 2, multicenter, open-label study evaluating the safety, tolerability, PK, PD, and effect on COAs of AL001 administered intravenously (96-week dosing period), in asymptomatic and symptomatic FTD-GRN mutation carriers and in symptomatic frontotemporal dementia patients with C9orf72 hexanucleotide repeat expansion mutations (FTD-C9orf72).

The study has two parts: A phase 2 open-label treatment period (Part 1), followed by an open-label extension (OLE) period (Part 2). Part 1 is a 96-week evaluation of the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and clinical effect of AL001 administered intravenously
(60 mg/kg, every 4 weeks [q4w]), for a total of 25 doses (96-week dosing period), in asymptomatic and symptomatic carriers of loss-of-function GRN mutations causative of FTD, and in symptomatic carriers of C9orf72 hexanucleotide repeat expansion mutations causative of FTD. Part 2 is an optional OLE for eligible participants who have completed the 96-week Part 1 treatment period. The OLE period will evaluate the long-term safety and tolerability of AL001 administered at the same dose and regimen as Part 1 (60 mg/kg, q4w), for up to a total of 25 doses (96-week optional OLE period).

Two cohorts will be enrolled: a GRN Cohort and a C9orf72 Cohort. Both cohorts will enroll symptomatic patients with FTD;
Frontotemporal dementia patients must have a diagnosis of possible or probably bvFTD or PPA.
All participants will be administered open-label, IV AL001 at the study site (over a 96-week dosing period). The primary objective of this Phase 2 study is to assess safety and tolerability of dosing of IV AL001. Secondary and exploratory objectives include evaluating the PK and the preliminary effect of AL001 on PD biomarkers and COAs in asymptomatic and symptomatic participants.

Intervention

The study will include a screening period (within 6 weeks prior to Day 1), a treatment period (96 weeks), and a follow-up period (8 weeks
after the last dose of AL001) with a follow-up visit at Week 105 (study

completion).

Study burden and risks

This study requires that the patient will visit the hospital 29 times over a period of 2 years. A visit will take 4 to 5 hours.

During the study, the following will take place:
- body weight.
- the patient receives the study drug
- AEs.
- record the use of medication and vitamin supplements
- physical examination.
- neurological examination.
- ECGs
- vital signs
- bloodsamples and collect urine
- We will ask the patient and study partner to complete several questionnaires. For some parts the patient will be asked to do some tasks like drawing or counting and one questionnaire is used to assess suicidal thoughts and behaviors
- lumbar punctures to collect cerebrospinal fluid.
- MRIs
- Pregnancy test from blood and urine will be performed if the patient is female of child bearing potential. The patient is not allowed to be pregnant in this study.

All drugs may cause certain side effects and discomforts. The most common discomforts are listed below. There may also be side effects and discomforts that are not yet known.

In the Phase 1 study, a total of 64 participants were enrolled. There are no serious side effects related to AL001 or study discontinuations because of any side effect. The most common discomforts reported from participants in studies with AL001 were headache, vomiting, lipase increase (measure of an inflamed or injured pancreas), anemia (low blood cell count), myalgia (muscle pain), and upper respiratory tract infection (infection of the nasal passages or sinuses).

There is a chance that the body will produce antibodies against AL001, that an infusion reaction will occur, or that a hypersensitivity reaction will be triggered.

The studies in the context of the study also have risks:
- Blood tests can hurt or cause a blood shed.
-Lumbar puncture can cause the following complaints and complications: headache, temporary numbness or pain in legs, back and neck pain, dizziness, fainting, pain at the location of the spinal catheter, inflammation or infection (in rare cases this can cause meningitis), bleeding and nerve damage.

Risks related to genetic testing: It is not inconceivable that the patient should answer questions about having a genetic test carried out when he / she applies for life or disability insurance. It cannot be excluded that the insurer will attach consequences to this. It could also be that during the inspection sometimes things are discovered that are not yet treatable

Contacts

Public
Alector Inc

131 Oyster Point Boulevard, suite 600
San Francisco CA94080
US
Scientific
Alector Inc

131 Oyster Point Boulevard, suite 600
San Francisco CA94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part 1: Protspective participants must meet all of the following criteria specific to their
applicable participant category. These bullet points are some of the important criteria within each category:
1) Completed Study AL001-1 through the Day 57 visit and did

not experience AEs that the investigator deems would prevent safe participation in Study AL001-2.
2) Meets 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible behavioral variant frontotemporal dementia (bvFTD; Rascovsky 2011) or has diagnosis of primary progressive aphasia (PPA; Gorno Tempini 2011)
3) Prospective participant is a carrier of a loss of function GRN mutation causative of
FTD-GRN
4) Is a carrier of a hexanucleotide repeat expansion C9orf72 mutation causative of FTD and knows their mutation status
5) Has a CDR® plus NACC global score of 0.5, 1, or 2; and 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD (Rascovsky 2011) or a diagnosis of PPA (Gorno Tempini 2011)
In addition, this is the list of the important inclusion criteria:
• Participants are 18 to 85 years of age.
• At screening, female prospective participants must be nonpregnant and nonlactating, and at least one of the following conditions must apply:
- Not a woman of childbearing potential (WOCBP) (either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1 year postmenopausal ([amenorrhea duration of 12 consecutive months with no identified cause other than menopause]).
- Participant is a WOCBP and using an acceptable contraceptive method from screening until 8 weeks after the last dose of study drug. Acceptable contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. In addition, total abstinence, in accordance with the lifestyle of the participant, is acceptable.
- A WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after final dose of study
intervention are located in the Schedules of Assessments (Table 14-1 and table 14-2 in
the protocol).
• Male prospective participants, if not surgically sterilized, must agree to use acceptable contraception and not donate sperm from Day 1 until 10 weeks after the last dose of study drug. Acceptable contraception for the male patient when having sexual intercourse with a WOCBP who is not currently pregnany is defined as using a condom. In addition, WOCBP partners must use hormonal
contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. In addition, total abstinence, in accordance with the lifestyle of the participant, is acceptable.
• Agrees not to donate blood or blood products for

transfusion for the duration of the study and for 1 year after final dose of study drug.
• Is willing and has the ability to comply with the study protocol.
• Is willing and able to give informed consent. If the study participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
• Has availability of a person ("study partner") who has frequent and sufficient contact with the participant (at least 5 hours per week of in person contact), can provide accurate information regarding the participant's cognitive and functional abilities as well as their health throughout the study, agrees to provide information at site visits that require partner input for COA completion, and signs the necessary consent form. (Note: asymptomatic participants require the study partner at the COA visits only; symptomatic participants require the study partner at each visit) Inclusion criteria applicable to those UK, US, or Canadian participants participating in the optional Winterlight Labs Speech Assessment (WLA) only:
-participant has available and willing study partner to administer the WLA
-participant has WiFi access in their residence or WiFi access in a private area where the testing can take place
-US, UK, or Canadian participants who are proficient in English in the investigator's opinion

Part 2: participants must complete Part 1, week 97
1.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 their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB or IEC.
2. Is willing and has the ability to comply with OLE requirements, in the opinion of the investigator.
3. Has availability of a person ("study partner") who can continue to assist with assessments throughout the OLE evaluation period. The study partner must have frequent and sufficient contact with the participant , and must have sufficient cognitive capacity; can be the same individual as in Part 1.

Exclusion criteria

Deel 1:
• History of severe allergic, anaphylactic, or

other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
• History of substance use disorder (drug or alcohol) within the past 2 years, with the exception of nicotine, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria (American Psychiatric Association 2013).
•Current acute illness or active infection requiring oral or IV antibiotics within 30 days prior to study drug administration that may affect safety assessments.
• History of surgery, hospitalization, or clinically significant infection requiring oral or IV antibiotics during the 30 days prior to screening.
• Has planned procedure or surgery during the study that would interfere with the ability to perform study assessments.
• History of seizures, with the exception of childhood febrile seizures.
• Has clinically, significant systemic immunocompromised condition because of continuing effects of immune suppressing medication.
• Has major depressive disorder or history of schizophrenia, schizoaffective disorder, or bipolar disorder.
• Has history of cancer
• Has history or presence of intracranial tumor that is clinically relevant.
• Has any clinically significant medical condition or laboratory abnormality that precludes the participant's safe participation in and completion of the study.
• Positive for hepatitis B surface antigen, hepatitis C virus antibodies, or human immunodeficiency virus 1 and 2 antibodies or antigen, or history of spirochetal infection of the CNS.
• Significant kidney disease as indicated by a screening creatinine clearance <30 mL/min as calculated by the central laboratory using the Cockcroft Gault formula, which remains <30 mL/min if retested.
• Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >= 2.5 the upper limit of normal (ULN) or total bilirubin >=2.0 × ULN, which remains above either of these limits if retested or other abnormalities in synthetic function that are clinically significant.
• Has, within the last 2 years, had unstable or clinically significant cardiovascular disease.
• Participant has uncontrolled hypertension.
• Participant has history or presence of an abnormal ECG that is clinically significant including complete left bundle branch block, secondor third degree heart atrioventricular block, or evidence of prior acute or subacute myocardial infarction or ischemia.
• Participant has QT interval corrected using Fridericia formula (QTcF)

Related Exclusion Criteria please refer to the protocol
Part 2:
Part 1 participants are not eligible for continued treatment with AL001 optional OLE if any of the following apply:
1. 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).
2. Part 1 participant has a CDR® plus NACC FTLD global score >2 during Part 1.
3. 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:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-11-2019
Enrollment:	11
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	06-06-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	01-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2024
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
EudraCT	EUCTR2019-00138-20-NL

Register	ID
ClinicalTrials.gov	NCT03987295
CCMO	NL70050.078.19