A Randomized, Double-blind, Placebo-controlled Single Ascending Dose and Open-label Multi-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ALN-APP in Adult Patients with Early-onset Alzheimer*s Disease (EOAD)

Published: 17-01-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-508363-79-00 check the CTIS register for the current data. Part AMain objectives: • To evaluate the safety and tolerability of single intrathecal (IT) doses of ALN-APP in adult patients with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Structural brain disorders
Study type	Interventional

Summary

ID

NL-OMON51311

Source
ToetsingOnline

Brief title
ALN-APP-001

Condition

- Structural brain disorders

Synonym
Dementia, memory loss

Research involving
Human

Sponsors and support

Primary sponsor: Alnylam Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: ALN-APP, Alzheimer, Pharmacodynamic, Pharmacokinetics

Outcome measures

Primary outcome

Part A - Single-dose Period:

To evaluate frequency of adverse events. Safety will also be evaluated through vital signs, physical exams, neurological assessment, cognitive and suicide severity assessment, neuroimaging, electrocardiograms (ECGs), and clinical laboratory assessments.

Part B - Multi-dose Period:

To evaluate frequency of adverse events. Safety will also be evaluated through vital signs, physical exams, neurological assessment, cognitive and suicide severity assessment, and clinical laboratory assessments.

Secondary outcome

Part A - Single-dose Period:

Change from baseline in levels of CSF sAPPα and sAPPβ and evaluate PK parameters of ALN-APP and of potential metabolites in plasma (area under the concentration-time curve [AUC], maximum plasma concentration [Cmax]), urine (fraction excreted in the urine [fe]) and CSF (concentration at time 't' [Ct]).

Part B - Multi-dose Period:

Change from baseline in levels of CSF sAPPα and sAPPβ and evaluate PK parameters of ALN-APP and of potential metabolites in plasma (area under the concentration-time curve [AUC], maximum plasma concentration [Cmax]), and CSF (concentration at time 't' [Ct]).

Study description

Background summary

This Phase 1 randomized, double-blind, placebo-controlled, single ascending dose and open-label multi-dose study is designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intrathecally administered ALN-APP in adult patients with Early-Onset Alzheimer*s Disease (EOAD).

Study objective

This study has been transitioned to CTIS with ID 2023-508363-79-00 check the CTIS register for the current data.

Part A
Main objectives:
• To evaluate the safety and tolerability of single intrathecal (IT) doses of ALN-APP in adult patients with EOAD

Part B
Main objectives:
• To evaluate the safety and tolerability of multiple IT doses of ALN-APP in

adult patients with EOAD.

Study design

This is a 2-part first-in-human Phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intrathecally administered ALN-APP in adult patients with EOAD. Part A will be a randomized, double-blind, placebo-controlled single-ascending dose (SAD) period and Part B will be a multi-dose open-label period including patients previously enrolled in Part A or their replacement who are allowed to enter Part B.

A single dose of study drug (ALN-APP or placebo) will be administered to each patient in Part A. Initially, 2 sentinel patients will be monitored for adverse events for at least 15 days prior to study drug administration to the remaining patients in the respective dose cohort. The decision to proceed to dosing the next cohort and the actual dose to be administered will be determined by the Safety Review Committee (SRC) based on postdose safety and tolerability data through at least Month 1 in addition to available PD and other data.

In Part B, up to 3 ALN-APP dosing regimens may be evaluated. Dosing regimen includes: (1) the dose level administered and (2) the dosing frequency. Dosing in Part B may begin when the SRC recommends the dosing regimen for the first cohort based on review of cumulative safety data and available PD data from at least 3 Part A cohorts through at least the Month 3 visit. Part B may start while the follow-up and/or dosing of certain Part A cohort(s) is ongoing.

The SRC will perform ongoing reviews of safety, tolerability, and available PK and PD data collected throughout the study.

Intervention

In Part A of the study four dose level cohorts will be enrolled sequentially, with each subject receiving a single dose of the study drug or a placebo. Subjects enrolled in group 1 and 2 will be randomized 4:2 to ALN-APP versus placebo. Subjects in group 3 and 4 will be randomized 6:2 to ALN-APP versus placebo. Each subject will receive a single dose.

Group: 1
Planned Dose of Study Drug (mg): 25
Ratio Study drugs:Placebo: 4:2
Total number of patients within group worldwide: 6

Group: 2
Planned Dose of Study Drug (mg): 75
Ratio Study drugs:Placebo: 4:2
Total number of patients within group worldwide: 6

Group: 3
Planned Dose of Study Drug (mg): 225
Ratio Study drugs:Placebo: 6:2
Total number of patients within group worldwide: 8

Group: 4
Planned Dose of Study Drug (mg): 600
Ratio Study drugs:Placebo: 6:2
Total number of patients within group worldwide: 8

Group: Optional
Planned Dose of Study Drug (mg): 900
Ratio Study drugs:Placebo: 6:2
Total number of patients within group worldwide: 8

Group: Optional
Planned Dose of Study Drug (mg): 1200
Ratio Study drugs:Placebo: 6:2
Total number of patients within group worldwide: 8

Group: Optional
Planned Dose of Study Drug (mg): <1200
Ratio Study drugs:Placebo: 6:2
Total number of patients within group worldwide: 8

For each dose escalation, the decision to proceed to dosing the next cohort and the actual dose to be administered will be determined by the SRC based on the review of postdose safety and tolerability data through at least Month 1, as well as RBANS score at Month 1, CBC with differential and CSF sAPPα and sAPPβ levels through Day 15, from at least 5 patients for Cohorts 1 and 2 (6 patients/cohort) and at least 6 patients for the remaining cohorts (8 patients/cohort), cumulative safety data (eg, if a safety signal is observed, then upon SRC recommendation, a de-escalation cohort may be initiated), and available PK and PD data.

The actual dose to be administered may be modified (higher, lower, or the same, but no more than 3-fold higher than the previous dose) from planned doses based on emerging safety, PK, and PD data from preceding cohorts. The actual dose of the optional cohorts will not exceed a 1.5-fold increment from the highest dose previously tested, and no dose will exceed the maximum dose of 1200 mg.

During part B subject will receive repeat doses over a 12-month period. The dose level and frequency will be based on review of part A data. No dose in Part B will exceed the highest dose in Part A. Informed consent for part B will be obtained separately.

Study burden and risks

Subjects will participate in Part A of the study for the duration of 14 months. Subjects will need to come to the hospital more often than they normally would and they undergo additional tests. These include physical and neurological examination, ECG*s, pregnancy tests, urine/blood tests and questionnaires. Subjects will receive medication via intrathecal injection and subjects cannot be pregnant at the start or during the study.

Aside from these interventions, participation in this study involves blood draws (venapunction) and in the course of 14 months, during 10 visits, 181ml blood will be taken. Additionally cerebrospinal fluid (CSF) samples collection of 20ml will be collected.

The study medication, ALN-APP, has not been previously administered in humans. Therefore, it is not known which risks are associated. However as with any study medication, the subject might experience an allergic reaction. These include the following symptoms: Hives, Rash, Itching, Flushing, Swelling of the lips, tongue or throat, Sudden shortness of breath, Decreased consciousness, Nausea, Vomiting, Decrease in blood pressure.

The study medication is administered via a needle inserted between two lumbar bones into the subjects lower spine: While this is a relatively safe procedure there are possible minor and major complications which can occur even when standard procedures are followed, and proper technique are used. These complications include: Headache, Back discomfort or pain, Radicular symptoms, Bleeding, Infection, In rare cases bleeding in the brain and development of tumors beneath the skin.

There may be other risks depending on the subjects specific medical condition, these include:
• Allergy-related reactions
• ECG risks: skin irritation is rare but could occur from the electrodes or gel that is used.
• PET-scan risks: we use radioactive materials which may cause damage to the subjects health
• MRI Risks
• Lumbar puncture risk

Scientific evidence generated over the last 3 decades implicates amyloid beta (Aβ) aggregation as an early event in the pathogenesis of Alzheimer*s disease (AD). Evidence suggests that reducing the production of APP and thereby reducing downstream APP cleavage products such as Aβ may be an effective therapeutic strategy for AD.

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

Inclusion Criteria for Participants in Part A and Replacement Patients in Parts A and B:
1. Male or female, aged 18 years or older at the time of informed consent
2. Individuals with mild cognitive impairment or mild dementia due to EOAD, where disease onset occurred at age <65 years, and AD diagnosis confirmed by CSF biomarkers or positive PET amyloid imaging
3. CDR global score 0.5 or 1.0 and Mini Mental State Examination (MMSE) >20
4. Able and willing to meet all study requirements: adequately supportive psychosocial circumstances, able to undergo Magnetic Resonance Imaging (MRI) scans and able to tolerate them, body Mass Index (BMI) >=18 and <=34 kg/m2 at Screening visit, able to tolerate LP and undergo PET
5. Patient is able to understand and is willing and able to comply with the

study requirements and to provide written informed consent

Inclusion Criteria for Participants Who Transition from Part A to Part B:
1. Able and willing to meet all study requirements in the opinion of the Investigator, including travel to study center, procedures, measurements and visits, including adequately supportive psychosocial circumstances, able to undergo Magnetic Resonance Imaging (MRI) scans and able to tolerate them, able to tolerate LP and undergo PET
2. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent

Exclusion criteria

Exclusion Criteria for Participants in Part A and Replacement Patients in Parts A and B:
1. Non-Alzheimer's disease dementia
2. Has any of the following laboratory parameter assessments at Screening: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2×upper limit of normal (ULN), total bilirubin >1.5×ULN, international normalized ratio (INR) >1.4, platelet count <100,000/microliter (µL), absolute neutrophil count normal (LLN) cells/µL or absolute lymphocyte count glomerular filtration rate (eGFR) <45 mL/min/1.73m2
3. Clinically significant ECG abnormalities at Screening
4. Has systolic blood pressure >150 mmHg and/or a diastolic blood pressure >90 mmHg after 10 minutes of rest at screening
5. Has known active human immunodeficiency virus (HIV) infection
6. Has active severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection
7. Treatment with another investigational drug, biological agent, or device within 6 months of Screening, or 5 half-lives of investigational agent
8. Use of the following medications is prohibited unless the dose has been stable for at least 12 weeks prior to Screening and the dose regimen is not anticipated to change during the study: antidepressants, antipsychotics, anxiolytics, benzodiazepines, acetylcholinesterase inhibitors, memantine
9. Supplement use (eg, coenzyme Q10, vitamins, creatine), unless stable dose for 6 weeks prior to Screening
10. Antiplatelet or anticoagulant therapy within the 28 days prior to Screening or anticipated use during the study
11. Oral carbonic anhydrase inhibitors
12. Treatment with amyloid-targeting antibody within the last 3 years prior to Screening
13. Treatment with another IT administered medication within the last 1 year prior to Screening
14. Active infection requiring systemic antiviral or antimicrobial therapy
15. Prior treatment with an siRNA or antisense oligonucleotide (ASO)

16. Any history of gene therapy or cell transplantation or experimental brain surgery
17. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
18. Any condition, including EOAD-related symptoms, that would prevent either writing or performing assessments
19. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening
20. Any condition that increases risk of meningitis (eg, immunodeficient state)
21. History of bleeding diathesis or coagulopathy
22. A medical history of brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment
23. History of uncontrolled seizures within the last 6 months prior to Screening
24. Hospitalization for any major medical or surgical procedure
25. Clinically relevant hematological, hepatic, cardiac or renal disease or event
26. History of intolerance to IT injection(s)
27. Is not willing to comply with the contraceptive requirements during the study period
28. Female patient is pregnant, planning a pregnancy, or breast-feeding and history of drug/chemical or alcohol abuse

Exclusion Criteria for Participants Who Transition from Part A to Part B:
1. Has any of the following laboratory parameter assessments at Screening: international normalized ratio (INR) >1.4, platelet count <100,000/microliter (µL), absolute neutrophil count absolute lymphocyte count 2. Clinically significant ECG abnormalities at Screening
3. Has systolic blood pressure >150 mmHg and/or a diastolic blood pressure >90 mmHg after 10 minutes of rest
4. Has known active human immunodeficiency virus (HIV) infection
5. Has active severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection
6. Treatment with another investigational drug, biological agent, or device within 6 months of Screening, or 5 half-lives of investigational agent
7. Use of the following medications is prohibited unless the dose has been stable for at least 12 weeks prior to Screening and the dose regimen is not anticipated to change during the study: antidepressants, antipsychotics, anxiolytics, benzodiazepines, acetylcholinesterase inhibitors, memantine
8. Supplement use (eg, coenzyme Q10, vitamins, creatine), unless stable dose for 6 weeks prior to Screening
9. Antiplatelet or anticoagulant therapy within the 28 days prior to Screening
10. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening, risk of meningitis, bleeding diathesis or coagulopathy, history of brain or spinal disease, uncontrolled seizures within the last 6 months, hospitalization for any major medical or surgical procedure, not willing to comply with the contraceptive requirements, Female patient is pregnant, planning a pregnancy,

or breast-feeding and drug/chemical or alcohol abuse.

Study design

Design

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):	19-10-2022
Enrollment:	14
Type:	Actual

Ethics review

Approved WMO Date:	17-01-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-08-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	CTIS2023-508363-79-00
EudraCT	EUCTR2021-003198-74-NL
CCMO	NL79863.000.22