A Phase 2b/3, Double-Blind, Randomised, Placebo-Controlled 48-week Safety and Efficacy trial of ANAVEX2-73 for the Treatment of Early Alzheimer*s Disease (AD).

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Primary Objectives:* Change from baseline to week 48 in cognition according to the Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog) compared to placebo.* Changes from baseline to week 48 in ability to perform daily activities according to the...

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

Summary

ID

NL-OMON54997

Source
ToetsingOnline

Brief title
ANAVEX2-73 AD study

Condition

- Mental impairment disorders
- Dementia and amnestic conditions

Synonym
Alzheimer's Disease, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Anavex Life Sciences Corp.
Source(s) of monetary or material Support: ANAVEX Life Sciences Corp.

Intervention

Keyword: Alzheimer's Disease, ANAVEX2-73, Mild cognitive impairment

Outcome measures

Primary outcome

The primary endpoints, ADAS-Cog and ADCS-ADL, and their corresponding change from baseline values will be summarized by visit and treatment group.

Differences between each active treatment group and placebo at week 48 will be assessed based on the LSMeans from a mixed effects repeated measures ANCOVA model with fixed effects for treatment group, visit, treatment by visit interaction, absence/presence of the rs1800866 or rs113895332/rs61143203 variants, and baseline value, and a random effect for subject.

Secondary outcome

Secondary efficacy endpoint:

For the changes in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB questionnaire) between baseline and week 48 compared to placebo similar statistical methods from the primary efficacy analysis (ADA-Cog and ADCS-ADL questionnaires) will be applied.

Sleep Assessment Analyses:

The main input measures from the sleep assessments are average sleep continuity values from the RSCAQ, the scale scores from the ISI and ESS, and the percent

of subjects per treatment group that endorse two or more symptoms per disorder cluster at a scale score of > 3. These values will be assessed for group differences (change from baseline to Week 48) between each active treatment group and placebo for each endpoint using a model similar to that proposed for the primary efficacy endpoint. An additional test comparing both active treatments to placebo will be conducted using the LSMeans from the ANCOVA model. The analyses will be conducted using the ITT Population.

Other Secondary Efficacy Analyses:

MMSE:

The derived MMSE variable is change from Baseline visit to Week 48. Descriptive analyses will be performed to describe the cognitive assessments. In addition, the derived efficacy variables will be tabulated by visit and by treatment. Change in cognition scores from baseline between two-treatment groups will be compared to determine whether there is a statistically significant difference.

The other analysis will be a descriptive analysis for responders, if data permit. Response is defined as a positive change in MMSE score. The analysis will include the number and % of responders for each dose group.

Other AD Relative Measures* Analyses:

- Zarit Burden Interview (ZBI)
- Quality of Life of Alzheimer*s Disease Patient and Caregiver Report (QoL-AD)

- Neuropsychiatric Inventory Questionnaire (NPI-Q)

- Clinical Global Impression of Severity (CGI-S)

- Clinical Global Impression * Improvement scale (CGI-I)

Two-sample t-tests at * = 0.05 will be used to test if there is a statistical significance of the change at each visit from baseline between each active treatment group and placebo and between both active groups and placebo if the intended metric is symmetrically distributed. Otherwise, the nonparametric Wilcoxon rank sum test will be used. There will be no correction to be made for multiple comparisons because of the exploratory nature of the data. Data will be tabulated by visit and by treatment.

MRI Related Endpoints:

* Based on available data, structural (and optional ASL) MRI scans assessments characteristic for AD pathophysiology from baseline and compared to placebo at +48 weeks.

* Change from baseline in whole brain structure and function, including measures of cortical thickness, and correlational maps and behavioral outcomes at end of study in ANAVEX 2-73 versus placebo treated subjects.

* Change from baseline in medial temporal cortex structure and function correlational maps and behavioral outcomes at end of study in ANAVEX 2-73 versus placebo treated subjects.

* Change from baseline in hippocampus structure and function correlational maps and behavioral outcomes at end of study in ANAVEX 2-73 versus placebo treated

subjects.

* Change from baseline in basal forebrain structure and function correlational maps and behavioral outcomes at end of study in ANAVEX 2-73 versus placebo treated subjects.

* Exploration of laterality effects on whole brain volumes and pre-defined regions of interest volumes at baseline and end of study after treatment with ANAVEX 2-73 versus placebo.

Two-sample t-tests at * = 0.05 will be used to determine statistical significance of the structural and optional ASL functional MRI data at week 48 from baseline between each active treatment group and placebo and between both active groups and placebo. Otherwise, a Wilcoxon rank sum test will be used.
The relationship between ANAVEX2-73 and CSF/serum and MRI parameters related to AD pathophysiology will also be explored.

Study description

Background summary

Cognitive deficits in patients Alzheimer's disease (AD) often involve dysregulation of neuronal signaling. This neuronal signaling imbalance may be countered by enhancing neuronal homeostatic mechanisms. Considering the high unmet medical treatment need for neurodegenerative diseases, novel therapeutic strategies, such as those targeting neuronal homeostatic mechanisms, could lead not only to improving acquisition or slowing progression of cognition but also of other neurologic functions.

ANAVEX2-73 is an investigational oral sigma-1 receptor (*1R) agonist whose mechanism of action is to activate the *1R, which in turn enhances cellular homeostasis by targeting mitochondrial dysfunction, including oxidative stress; protein misfolding; autophagy, neuroinflammation; and other cellular stress

responses, known to be implicated in neurodegenerative disorders. ANAVEX2-73 has been shown pharmacologically to be an effective neuroprotective, anticonvulsive, and anti-depressant therapeutic agent.
ANAVEX2-73 has shown to significantly improve cognitive functions in various experimental pre-clinical models.

Because of its targeted upstream mechanism of action, ANAVEX2-73 is assumed to be potentially disease modifying for Alzheimer's Disease and potentially possessing a better safety profile than currently approved drugs.

ANAVEX2-73 has been studied in animal models as well as normal volunteers and patients with mild to moderate AD. In general, ANAVEX2-73 has a favorable safety profile, with the majority of TEAEs associated with daily oral doses of 50 mg or greater. Furthermore, these studies support ANAVEX2-73*s long-term efficacy and the possibility of using precision medicine approaches for the treatment of AD and other neurodegenerative and neurodevelopmental disorders.

Given the current lack of approved treatment options with acceptable side effect profiles for AD, the development of ANAVEX2-73 could meet this critical unmet medical need for AD patients.

Study objective

Primary Objectives:
* Change from baseline to week 48 in cognition according to the Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog) compared to placebo.
* Changes from baseline to week 48 in ability to perform daily activities according to the Activities of Daily Living Scale (ADCS-ADL) compared to placebo.

Secondary Objectives:
* Change from baseline to week 48 on Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) compared to placebo.
* To establish safety and tolerability of ANAVEX2-73 in AD patients.
* To evaluate whether ANAVEX2-73 improves sleep continuity as assessed on a serial basis (weeks 0, 4, 12, 24, 36, and 48) with a questionnaire that assess retrospectively reported sleep continuity (RSCAQ) and the Insomnia Severity Index (ISI).

Further AD-related Objectives
* Changes on the Neuropsychiatric Inventory Questionnaire (NPI-Q) at week 48 compared to placebo.
* Change in dementia symptom severity according to the Mini-Mental-State Examination (MMSE) at week 48 compared to placebo.
* Changes in Quality of Life of the patient and caregiver according to the Quality of Life of Alzheimer*s Disease Patient and Caregiver Report (QoL-AD) at week 48 compared to placebo.

* Changes in the level of burden experienced by caregivers according to the Zarit Burden Interview (ZBI) at week 48 compared to placebo.
* Clinical Global Impression of Severity (CGI-S) at week 48 compared to placebo.
* The Clinical Global Impression * Improvement scale (CGI-I) at week 48 compared to placebo.
* Structural and optional Arterial Spin Labeling (ASL) MRI scan assessments characteristic for AD pathophysiology from baseline and compared to placebo at week 48.
* Blood assessnt from baseline and compared to placebo at week 48: Abeta40, Abeta42, T-tau, NF-L, YKL-40, BACE1, Glutamate and related metabolites concentrations,
* Changes in CSF parameters (Abeta40, Abeta42, T-tau, P-tau, NFL, YKL-40, neurogranin, BACE1 concentration) characteristic for AD pathophysiology from baseline and compared to placebo at week 48 (except for participants in Australia and in the UK).
* AD relevant pre-specified genetic variants will be assessed. Statistical testing of treatment differences within subgroups will be performed.

Further Sleep-related Endpoints
* Longitudinally evaluate changes in sleep disorders symptomatology and daytime sleepiness as assessed with repeated single point assessments: (1) the Sleep Disorders Symptom Check List (SDS-CL-25) and the (2) Epworth Sleepiness Scale (ESS), both evaluated at weeks 0, 4, 12, 24, 36, and 48.

Study design

This is a Phase 2b/3, randomized, placebo-controlled, double-blind, 48-week study to evaluate the effects of ANAVEX2-73 on cognition and functioning after 48 weeks of daily treatment. Additional outcome measures include refined measures of sleep and behavioral symptoms typically observed in AD, changes in daily functioning of participants and changes in caregiver burden, as well as changes in quality of life measures of both, patients and caregivers during treatment with ANAVEX2-73. In addition, safety assessments, pharmacokinetic (PK) assessments and collections of CSF and blood markers of AD pathophysiology before and after treatment will be performed.

The study design requires about 450 patients with early AD and will follow the below medication schedule.

* Randomization to three parallel groups (placebo, ANAVEX2-73 30 mg/day, and ANAVEX2-73 50 mg/day).
* Treatment: 48-week treatment will include:
- A gradual 3-week titration period with incremental increase of 10 mg per week for the first 3 weeks (Week 1: placebo, or ANAVEX2-73 10 mg/day; Week 2: placebo or ANAVEX2-73 20 mg/day and then Week 3: placebo or ANAVEX2-73 30 mg/day), and a final 20 mg/day increase to ANAVEX2-73 50 mg/day for the 50 mg group.

- A maintenance period (Week 4 to Week 48): of placebo, or ANAVEX2-73 30mg/day or ANAVEX2-73 50mg/day .
* During the up-titration phase:
- Dose reduction will be allowed for Adverse Events or tolerability concerns.
- Participants may remain at 10 mg/day for stabilization or for possible drug-related AEs to resolve but should attempt to re-titrate to their target dose once their AE has resolved.
- If a patient is not able to tolerate a dose, the study investigator should contact the safety and medical monitor for resolution.

* During the maintenance phase:
- Subjects should be able to tolerate the lowest maintenance dose (10 mg) directly or after a dose reduction. If not able to maintain a dose of 10 mg/d or higher then they will be taken off the study drug and will complete the Early Terminatin Visit.
- Participants who experience any dose interruption equal > 10 consecutive days must be withdrawn from the study.

Safety and tolerability will be assessed throughout the study, starting from the first dose of study medication.

Intervention

3 treatment arms will be used in this study. Subjects will be randomly assigned to a treatment arm with a 1:1:1 ratio:
The study medication and placebo are delivered as capsules and have the same appearance.
ANAVEX2-73 capsules are available in the dose of 10 mg and 20 mg.

- ANAVEX2-73 arm: 30 mg/day QD;
- ANAVEX2-73 arm: 50 mg/day QD;
- Placebo arm

As of baseline there will be a two week titration period.
The ANAVEX2-73 30 mg arm starts with 10 mg/day for one week then 20 mg/day for one week to reach the 30 mg/day.
The ANAVEX2-73 50 mg arm starts with 10 mg/day for one week then 20 mg/day for one week then 30 mg/day for one week to reach the 50 mg/day.

The study medication/ placebo will be taken once daily for a period of 48 weeks.

Study burden and risks

Currently there are no well-developed treatment menthods for people who are

diagnosed with Alzheimer*s Disease. The development of ANAVEX2-73 could meet the critical unmet medical need for AD patients.

ANAVEX2-73 will be delivered as capsules for oral intake.

Side effects of ANAVEX2-73 are: dizziness, headache, euphoric mood, depression like syndrome and gastrointestinal disorders like nausea, vomiting, diahrroea and constipation.

Risk associated to study assessments:
ECG: redness and itching caused by the sticky pads.
Blood draws: discomfort, bruising, minor infection or bleeding.
Lumbar punction: discomfort or pain during the procedure. There could also be an infection, nerve damage, bleeding into the spinal cord or headache.
MRI scan: claustrophobia
PET scan: radiation exposure which could later to cancer in future.

The following procedures are performded:
- Measurement of vital signs * all visits;
- Physical and neurological examination * screening, baseline and week 48;
- ECG * screening, baseline, week 24 and week 48;
- Lumbar puncture * screening and week 48 (for biomarker assessment and possibly at screening for AD diagnosis);
- Blood draws:
- clinical chemistry and hematology * screening, baseline, week 24 and week 48;
- AD biomarkers * screening, baseline and week 48;
- DNA/RNA * baseline and week 48 (RNA sampling only);
- Pharmacokinetics: 1x pre-dose and 1x post-dose * baseline, week 24 and week 48 (only post-dose);
- Standard urine analysis * screening, baseline, week 24 and week 48;
- Urine drug screen * screening and baseline;
- MRI for brain structure and function * baseline and week 48 (optionally followed by an ASL MRI on both visits);
- Questionnaires * during all visits multiple questionnaires will be completed, with or without the help of the caregiver.

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

1. Patients aged 60 to 85 years, inclusive, with a NIA-AA diagnosis of mild cognitive impairment (MCI) due to AD or early stage mild dementia due to AD. AD diagnosis must be made by an appropriately qualified board-certified or equivalent medical specialist.
2. At least one of the following criterion must be utilized to support AD diagnosis:
a. Historical records of amyloid CSF assessment or
b. Historical records of PET scan (amyloid scan or FDG-PET) or
c. Historical CT or MRI scan within 18 months of screening,
which are consistent with a diagnosis of AD. CSF collection would be required as part of the screening process unless historical records (CSF or PET) are available, except for participants in Australia and United Kingdom (UK).
3. Mini Mental State Examination (MMSE) score between 20-28, inclusive at both the Screening Visit and the Randomization Visit.
4. Free Recall score *17 or Total Recall score <40 on the Free and Cued Selective Reminding Test (FCSRT).
5. Participants are either outpatients, or residents of an assisted-living facility. Participant has a designated study partner, who spends at least 10 hr per week with the participant, in order that assessments (e.g., carer burden instruments) are completed with true knowledge of the participant.

6. No suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months (i.e. active suicidal thought(s) with intent but without specific plan, or active suicidal thought(s) with plan and intent) OR suicidal behavior in the past 2 years (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
7. If taking an acetylcholinesterase inhibitor or other AD medication (e.g. memantine), or OTC supplements/nutraceuticals used to treat AD, dose(s) must be stable for at least 90 days before screening.
8. If taking a psychoactive or anti-seizure medications, dose must be stable for at least 90 days prior to screening.

Exclusion criteria

1. Patients who have a progressive medical or neurological condition that in the opinion of the investigator would interfere with the conduct of the study. Exception: If diagnosed with seizures, must be on stable anti-seizure medication for at least 3 months prior to screening.
2. Current clinically significant systemic illness that is likely to result in deterioration of the patient*s condition or affect the patient*s safety during the study.
3. History or clinically evident stroke or clinically significant carotid or vertebrobasilar stenosis or plaque.
4. History of neurologic (e.g., stroke, traumatic brain injury) or psychiatric condition that the investigator deems may interfere with interpretability of data.
5. History of untreated thyroid disorder, Type 1 diabetes, and insulin dependent or uncontrolled Type II diabetes, as determined by the investigator (e.g., non-insulin-controlled Type II diabetes, whose HbA1c value is higher than 8.0%).
6. If a participant has a Body Mass Index (BMI) > 35, no co-morbidities, related to weight that would preclude participation in the study in the opinion of the investigator.
7. History of clinical hepatic dysfunction.
8. Current symptomatic and unstable/uncontrolled gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hematological or hormonal disorders.
9. Indication of liver disease, defined by serum levels of ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3x upper limit of normal (ULN) as determined during screening.
10. Significant history of drug addiction (with the exception of nicotine dependence) or abuse (including alcohol, as defined in DSM-5 or in the opinion of the investigator) within the last two years prior to informed consent, or a positive urine drug screen for cocaine, opioid, phencyclidine (PCP), amphetamine or marijuana at screening. Prescription medication yielding a positive drug screen are acceptable except for tricyclic antidepressants (e.g.,

Amitriptyline, Amoxapine, Desipramine, (Norpramin) Doxepin, Imipramine (Tofranil), Nortriptyline (Pamelor), Protriptyline (Vivactil), Trimipramine (Surmontil)).
11. Clinically significant infection within the last 30 days prior screening (e.g., chronic persistent or acute infection, urinary tract infections (UTI)).
12. Treatment with tricyclic antidepressants 60 days weeks prior to screening.
13. Treatment with immunosuppressive medications (e.g., systemic corticosteroids), within 90 days prior to screening (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted), or chemotherapeutic agents for malignancy within the last 3 years.
14. Myocardial infarction within the last year.
15. History of cancer within the last 3 years, with the exception of basal cell carcinoma and non-metastatic squamous cell carcinoma of the skin and prostate cancer with currently normal PSA.
16. Other clinically significant abnormality on physical, neurological, laboratory, or electrocardiogram (ECG) examination (e.g., atrial fibrillation) that could compromise the study or be detrimental to the participant.
17. Hemoglobin < 11 g/dL.
18. Smoking > 1 pack of cigarettes per day (as assessed for the 30 days prior to screening).
19. Alcohol use of more than 2 drinks per day.
20. Current use of over-the-counter (OTC) supplements or nutraceuticals unless they are on stable dose for at least 3 months prior to screening and are documented in the eCRF.
21. Use of over the counter (OTC) or prescription medication for sleep on 2 or more occasions per week.
22. Being treated with psychoactive medications on a stable dose for less than 3 months.
23. Any prior exposure to ANAVEX2-73.
24. Individuals enrolled in previous AD clinical trial involving an investigational drug treatment less than 3 months ago (longer than 3 months ago allowed).
25. Any known hypersensitivity to any of the excipients contained in the study drug formulation.
26. Any other criteria (such as a clinically significant screening blood test result), which in the opinion of the Investigator causes the participant not to qualify for the study.
27. Evidence of cerebrovascular dementia with a Hachinski score of 4 or more.
28. Use of St. John*s wort within 30 days of screening.

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:	Recruitment stopped
Start date (anticipated):	19-08-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Blarcamesine
Generic name:	ANAVEX2-73

Ethics review

Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2019-003302-27-NL
CCMO	NL72333.056.19
Other	NTC03790709