Open label extension study for patients with early Alzheimer's Disease (AD) enrolled in study ANAVEX2-73-AD-004

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Primary objective:To continue assessing the safety and tolerability of ANAVEX2-73.Safety and Tolerability Measures:* Physical examination* Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP],...

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

Summary

ID

NL-OMON50754

Source
ToetsingOnline

Brief title
ANAVEX2-73-AD-EP-004

Condition

- Mental impairment disorders

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

To continue assessing the safety and tolerability of ANAVEX2-73.

Safety and Tolerability Measures:

* Physical examination

* Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP],

diastolic blood

pressure [DBP], pulse oximetry, and oral body temperature)

* Graded AEs according to common Terminology Criteria for Adverse Events

(CTCAE) V4.0.3

* 12-lead ECG

* Columbia-Suicide Severity Rating Scale (C-SSRS)

* Clinical laboratory tests (hematology including coagulation, clinical

chemistry

including lipid panel, and urinalysis)

* Concomitant medication log

Secondary outcome

* Observation of P-tau blood level concentration

* To determine whether ANAVEX2-73 modifies cognition, behavior, or QoL,

according to the following standardized measures commonly used in AD:

- Change from baseline to week 96 in ADAS-Cog

- Change from baseline to week 96 in ADCS-ADL

- Change from baseline to week 96 in MMSE

- Change from baseline to week 96 in NPI-Q

- Change from baseline to week 96 in ZBI

- Change from baseline to week 96 in QoL-AD

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. Of interest was the observation from the Phase 2a in AD study showing beneficial effects of ANAVEX2-73 on insomnia, agitation and anxiety at 31 weeks

identified by the HAM-D item scores, which might suggest an additional important role of ANAVEX2-73 for the amelioration of behavioral and psychological symptoms of dementia (BPSD). Accordingly, sleep continuity and sleep disorders symptomatology will be assessed on a periodic basis for the duration of the proposed trial using self-report instruments.

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 objective:
To continue assessing the safety and tolerability of ANAVEX2-73.
Safety and Tolerability Measures:
* Physical examination
* Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse oximetry, and oral body temperature)
* Graded AEs according to common Terminology Criteria for Adverse Events (CTCAE) V4.0.3
* 12-lead ECG
* Columbia-Suicide Severity Rating Scale (C-SSRS)
* Clinical laboratory tests (hematology including coagulation, clinical chemistry including lipid panel, and urinalysis)
* Concomitant medication log

Secondary objective:
* Observation of P-tau blood level concentration
* To determine whether ANAVEX2-73 modifies cognition, behavior, or QoL, according to the following standardized measures commonly used in AD:
- Change from baseline to week 96 in ADAS-Cog
- Change from baseline to week 96 in ADCS-ADL
- Change from baseline to week 96 in MMSE
- Change from baseline to week 96 in NPI-Q
- Change from baseline to week 96 in ZBI
- Change from baseline to week 96 in QoL-AD

Study design

This is a Phase 2b/3 open-label extension study to evaluate the effects of ANAVEX2-73 on safety and efficacy (cognition) after 96 weeks of daily treatment. Additional outcome measures include measures of function and behavioral symptoms typically observed in AD during treatment with ANAVEX2-73.

The study is limited to subjects who completed the ANAVEX2-73-AD-004 double-blind clinical study who consent to enroll in the open label study. The

dosing schedule is as follows:
• Up-Titration over 10 weeks and then maintenance at either 50 mg daily or best tolerated dose.
• All patients regardless of their prior dose during the ANAVEX2-73-AD-004 clinical trial will undergo the following titration schedule: Treatment will begin at 10 mg/day ANAVEX2-73 for the first two weeks (Week 0 and Week 1), increasing by 10 mg every two weeks over a 10-week period to a maximum maintenance daily dose of either 50 mg or best tolerated dose*.
• Maintenance (Weeks 11-96): Subjects will take 50 mg ANAVEX2-73 per day or best tolerated dose*.
* Best tolerated dose will be determined during the titration period based on the basis of tolerability. Dosing adjustments (such as a dose decrease) may occur at any time under the supervision of the investigator. Patients should be maintained on the best tolerated ANAVEX2-73 daily dose between 20 mg - 50 mg. Should the patient continue to experience adverse events (AE) at the 20 mg/day dose, a dose of 10 mg/day (or temporary drug holiday) will be allowed under the guidance of the investigator.

Safety and tolerability will be assessed throughout the study, starting from the first dose of study medication. Participants who experience any dose interruption >= 10 consecutive days must be withdrawn from the study.

If the roll-over visit into this study occurs in clinic on the same day as the AD-004 doubleblind study End of Treatment Visit, the final double-blind dose should be taken in clinic on this day and the first dose of the open-label extension study should then be taken at home the following day.

Intervention

The research medication is ANAVEX2-73.

Treatment will begin at 10 mg/day ANAVEX2-73 for the first two weeks (Week 0 and Week 1), increasing by 10 mg every two weeks over a 10-week period to a maximum maintenance daily dose of either 50 mg or best tolerated dose.

The study medication will be taken once daily.

Study burden and risks

Currently there are no well-developed treatment methods for people who are diagnosed with Alzheimer*s Disease. The development of ANAVEX2-73 could meet critical unmet medical need for AD patients.

ANAVEX2073 will be delivered as capsules for oral intake.

Side effects of ANAVEX2-73 are: Dizziness, Headache, Disorientation, Fatigue,

Drowsiness, Gastrointestinal (stomach) disorders, like nausea, vomiting, diarrhoea and constipation, Hallucinations, Anxiety, Agitation, Delirium.

Risk associated to study assessments:
ECG: redness and itching caused by the sticky pads.
Blood draws: discomfort, bruising, minor infection or bleeding.

The following procedures are performed:
- Measurement of vital signs - all visits;
- Physical and neurological examination - all visits;
- ECG - all visits;
- Blood draws for safety and P-tau blood level concentration - all visits;
- Urinalysis and urine drug screen - all visits;
- Questionnaires ADAS-Cog and ADCS-ADL - at baseline and week 48;
- Questionnaires MMSE, ZBI, NPI-Q, QoL-AD and C-SSRS - all visits.

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. Previous completion of participation in the ANAVEX2-73-AD-004 double-blind study.
2. Participants may be either outpatients, or residents of an assisted-living facility.
3. Participants must have a designated study partner, who spends at least 10 hr per week
with the participant, in order for assessments (e.g., carer burden instruments) to be
completed with sufficient knowledge of the participant.
4. No suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (CSSRS)
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).
5. Confirmation from the participant that, if of childbearing potential, is not pregnant
through urine pregnancy testing.

Exclusion criteria

1. Adverse events (AEs) from the previous study (ANAVEX2-73-AD-004) that have not resolved, are moderate or severe, judged to be possibly related or related to study
drug, and considered by the investigator to be a contraindication to extension study
participation.
2. Any condition or laboratory abnormality that would make the subject, in the judgment
of the investigator, unsuitable for the study.
3. 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 baseline. Prescription medication yielding a positive drug screen are acceptable except

for
tricyclic antidepressants.
4. Any known hypersensitivity to any of the excipients contained in the study drug
formulation.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-03-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	07-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2023
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	EUCTR2021-004325-80-NL
ClinicalTrials.gov	NCT04314934

Register	ID
CCMO	NL79007.056.21