A double-blind, randomized, placebo-controlled, Multiple Ascending Dose (MAD) study in healthy elderly volunteers and Alzheimer's Disease (AD) and Parkinson's disease (PaD) patients to investigate the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) effects of multiple intravenous infusions of NX210c

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Part A (Healthy volunteers)Primary:• To assess safety and tolerability of multiple doses of NX210cSecondary• To evaluate the pharmacokinetic (PK) profile of NX210c in plasma after multiple doses. • To evaluate the exposure of NX210c in cerebrospinal...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53584

Source
ToetsingOnline

Brief title
MAD study of NX210c

Condition

- Neurological disorders NEC

Synonym
Alzheimer□s Disease, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Axoltis Pharma
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Alzheimer's Disease, Healthy elderly volunteers, Parkinson's disease, Pharmacokinetics/Pharmacodynamics

Outcome measures

Primary outcome

• Severity and incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), infusion related reactions (IRRs), clinical laboratory tests, ECGs, MRI (T1/T2), vital signs, physical and neurological examination, occurrence of anti-drug antibody (ADA) if applicable

Secondary outcome

• NX210c PK parameters per profile: Cmax, Tmax, AUC0-last, AUC0-inf, T1/2 , CL, Vz

• Cmax, blood to CSF ratio

• Severity and incidence of TEAEs

Study description

Background summary

The prevalence of neurocognitive disorders (NCD), including neurodegenerative diseases (NDDs) such as Alzheimer*s disease (AD) and Parkinson*s disease (PaD) is increasing, partly as a result of the extended life span of individuals. NDDs are most common and prevalent in elderly people worldwide and cause progressive neuronal dysfunction, toxicities, and death. These diseases lead to an irreversible weakening of all brain functions. The cognitive function in patients is seriously affected during these disease*s progression, the most important changes being declines in cognitive tasks that require to quickly process or transform information to make decisions, including measures of speed of processing, working memory, and executive cognitive function.

NX210c is a chemically synthesized cyclized peptide of 12 natural amino acids. Its linear form, the NX210 is derived from the subcommissural organ-spondin (SCO-spondin), a glycoprotein that is secreted by the SCO of the brain during embryogenesis. The SCO-spondin is strongly involved in neuronal development and neuroprotection. Due to immediate oxidation in blood and the consequent formation of a disulfide bridge between the two cysteine residues, the NX210 peptide can take a cyclic conformation, and is then called cyclic NX210 (NX210c).

Preclinical in vitro and in vivo data have shown that NX210c exhibits important properties, which may be suitable for the treatment of neurological disorders in humans (i.e., neuroprotection, neuro-regeneration, synaptic transmission, cognition, anti-neuroinflammatory action, and reduction in BBB permeability).

Part A of the present study will investigate the safety and tolerability of multiple intravenous infusions of NX210c with two ascending doses as well as NX210c pharmacokinetics (PK), the recommended dose for patients (RD) and pharmacodynamics (PD) effects, in healthy elderly subjects. Two subsequent cohorts enrolling Alzheimer and Parkinson's patients to further evaluate NX210c will then ensue in Part B.

Study objective

Part A (Healthy volunteers)
Primary:
• To assess safety and tolerability of multiple doses of NX210c

Secondary
• To evaluate the pharmacokinetic (PK) profile of NX210c in plasma after multiple doses.
• To evaluate the exposure of NX210c in cerebrospinal fluid after multiple doses

• To define the recommended dose for patients

Part B (AD and PaD patients)
Primary
• To assess safety and tolerability of multiple doses of NX210c

Secondary
• To evaluate the pharmacokinetic (PK) profile of NX210c in plasma after multiple doses.
• To evaluate the exposure of NX210c in cerebrospinal fluid after multiple doses

Study design

A double-blind, randomized, placebo-controlled, multiple ascending dose (MAD) study in healthy elderly volunteers and subsequently in patients with Alzheimer*s Disease (AD) and patients with Parkinson*s disease (PaD) to investigate the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) effects of multiple intravenous infusions of NX210c. Two doses will be investigated (5 mg/kg and 10 mg/kg) in the healthy elderly volunteers. The patients will be enrolled after 30 elderly healthy volunteers and following the recommendation of the Safety Review Committee (SRC). The dose investigated will be the one recommended for patients by the SRC.

Intervention

Investigational drug
NX210c prepared in glucose 5% at a concentration of 10 mg/mL for intravenous infusion of 5 mg/kg (Part A cohort 1) or 10 mg/kg (Part A cohort 2) in 10 minutes.

Comparative drug
Glucose 5% for intravenous infusion in 10 minutes.

Study burden and risks

Following the first phase 1 study in healthy volunteers conducted, and based on pre-clinical data, NX210c peptide combines multiple properties in one single drug. Taken together, all the potential beneficial effects of NX210c are promising elements to improve cognitive functions in patients with NCD.
The single ascending dose phase 1 study showed a good safety and tolerability profile of the NX210 administered by IV route in adult healthy volunteers irrespective of the received dose, including the highest ones at 5 and 10 mg/kg which are planned for the current MAD study.

NX210c was rapidly eliminated, and PD effects seemed to be long. The PD results provide encouraging elements of NX210 effect on the CNS via its metabolite NX210c.

The current MAD study design has been used previously in many clinical phase 1 studies; it includes a sentinel dosing for each cohort and a follow up visit 2 weeks after the last received dose for safety assessment.

A Safety Review Committee (SRC) will be set up in view to monitor closely safety, relevant available PK data and PD data in order to ensure that the study drug does not pose undue risk to subjects, in particular the SRC will decide on the next dose escalation and to select the dose to be investigated in the AD and PaD cohorts (at the SRC recommended dose).

All study drug administrations will be done in the clinic under medical supervision and dedicated to phase 1 studies. The subjects receiving any study drug will remain in the clinic for at least 2 hours after each study drug administration. Thus, the subjects can be closely monitored for any adverse signs during the study period .

Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.
The current study has been designed to confirm the good safety and tolerability profile of NX210c with repeated injections, define its pharmacokinetics with repeated injections, and define the dose to be used in target population such as Alzheimer*s Disease (AD) and Parkinson's Disease (PaD) patients.

It intends also to collect potential first signals effects of the NX210c via pharmacodynamics parameters at this selected dose in view to design appropriately future phase 2 trials in the target population where the NX210c may be beneficial on cognitive functions.

In each subject a lumbar puncture will be performed twice. Only trained physicians will perform these following strict procedures using adequate equipment (non traumatic needles) to minimize burden.

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

Participants are eligible to be included in the study only if all of the following criteria apply:
Part A:
1. Signed informed consent prior to any study-mandated procedure.
2. Healthy adult male or female participants, as determined by the Investigator, based upon a medical evaluation including medical history, physical examination, neurological examination, MMSE, MRI, lab tests and ECG.
3. Aged >= 55 years, inclusive at screening, and with a maximum weight of 110 kg.
4. Body mass index (BMI) between 18 and 32 kg/m2, inclusive at screening.
5. MMSE score of >= 25 at screening.
6. Able to communicate well with the Investigator and staff in the Dutch language and willing to comply with the study restrictions.
7. For female participants: only women of non-childbearing potential (WONCBP) can participate in this study. WONCBP have either undergone surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy; participant reported information) at least 90 days prior to baseline or are postmenopausal (amenorrheic for > 12 consecutive months before screening, confirmed by FSH levels > 26 IU/L). Essure® fallopian tube coil placement is not accepted as surgical sterilization because of the high failure rate.
8. For male participants: When engaging in sexual intercourse with WOCBP, the

male participant must use a male barrier method such as a latex or polyurethane condom from the start of dosing throughout the clinical study period, and for 90 days after the final administration of study intervention.
9. For male participants: The participant must not donate sperm at any time from the start of dosing, throughout the clinical study period, and for 90 days after the final administration of study intervention.

Part B (AD and PaD patients):
All patients:
1. Signed informed consent prior to any study-mandated procedure.
2. Aged >=55 years old, inclusive at screening, and with a maximum weight of 110 kg.
3. Body mass index (BMI) between 18 and 32 kg/m2, inclusive at screening.
4. Able to communicate well with the Investigator and staff in the Dutch language and willing to comply with the study restrictions.
5. Ability to walk, at least with an assistive device.
6. Living independently and not in an institution. Home care is allowed.
7. Have stable permitted medications for 4 weeks prior to dosing.
8. For female participants: only women of non-childbearing potential (WONCBP) can participate in this study. WONCBP have either undergone surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy; participant reported information) at least 90 days prior to baseline or are postmenopausal (amenorrheic for > 12 consecutive months before screening, confirmed by FSH levels > 26 IU/L). Essure® fallopian tube coil placement is not accepted as surgical sterilization because of the high failure rate.
9. For male participants: When engaging in sexual intercourse with WOCBP, the male participant must use a male barrier method such as a latex or polyurethane condom from the start of dosing throughout the clinical study period, and for 90 days after the final administration of study intervention.
10. For male participants: The participant must not donate sperm at any time from the start of dosing, throughout the clinical study period, and for 90 days after the final administration of study intervention.

AD patients only:
11. Meet diagnostic criteria for Alzheimer's Disease according to the National Institute on Aging (NIA) and the Alzheimer's Association published guidelines (NIA-AA) 2018, confirmed by cerebrospinal fluid analysis.
12. A brain MRI prior to study inclusion consistent with the clinical diagnosis of AD and without findings of significant exclusionary abnormalities.
13. A MMSE score van >= 20

PaD patients only:
11. A diagnosis of PaD, confirmed by a neurologist.
12. Hoehn & Yahr Stage <= III at Screening.
13. A brain MRI prior to study inclusion consistent with the clinical diagnosis

of PaD and without findings of significant exclusionary abnormalities.

Exclusion criteria

Participants who meet any of the following criteria will be excluded from study entry:
Part A:
1. Evidence of any history, or any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse irate, body temperature and 12-lead electrocardiogram (ECG)). Minor deviations from the normal ranges may be accepted, if judged by the Investigator to have no clinical relevance.
2. History of any known neurologic disease, cognitive impairment, or diagnosed decline in cognitive function abnormal related to the age, or history of seizure, (significant) head trauma, loss of consciousness, or significant neuroimaging findings, including but not limited to any previously known or discovered abnormalities on screening brain MRI that evoke other neurological diagnosis indicative of clinically significant abnormality.
3. Currently active known psychiatric disease or usage of anti-psychotic medications, anti-depressants drugs, addiction to drugs or alcohol, positive answer at screening to item 4 or 5 on the Colombia-Suicide Severity Rating Scale (C-SSRS) or suicidality which could pose a risk to study participation or determination of the endpoints, as judged by the investigator
4. Presence of a clinically significant infection in the judgment of the Investigator, within 7 days of baseline.
7. Any clinically significant abnormalities in laboratories (e.g. aspartate aminotransferase (AST) >2 × upper limit of normal (ULN); alanine aminotransferase (ALT) >2 × ULN; total bilirubin >2 × ULN; serum creatinine >2.0 × ULN, coagulation disorders including platelet count <100 × 103/µl) at screening or baseline. Measurements may be repeated at the investigator*s discretion.
8. Glomerular filtration rate (GFR) of <60 mL/min as estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at screening or baseline. Measurements may be repeated at the investigator*s discretion.
11. Abnormal findings in the resting ECG at screening or baseline (measurements may be repeated at the investigator*s discretion)

Part B (AD and PaD patients):
All patients
1. Clinically significant abnormalities, as judged by the investigator, in test results (including blood chemistry, hematology, virology, urine, medical history, physical examination, vital signs (systolic and diastolic blood

pressure, pulse rate, body temperature and 12-lead electrocardiogram (ECG)). Minor deviations from the normal ranges may be accepted, if judged by the Investigator to have no clinical relevance. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant.
2. Currently active known psychiatric disease or usage of anti-psychotic medications, anti-depressants drugs, addiction to drugs or alcohol, positive answer to item 4 or 5 on the Colombia-Suicide Severity Rating Scale (C-SSRS) or suicidality which could pose a risk to study participation or determination of the endpoints, as judged by the investigator.
3. Presence of a clinically significant infection in the judgment of the Investigator, within 7 days of baseline.
4. Any clinically significant abnormalities in screening laboratories (e.g., aspartate aminotransferase (AST) >2 × upper limit of normal (ULN); alanine aminotransferase (ALT) >2 × ULN; total bilirubin >2 × ULN; serum creatinine >2.0 × ULN).
5. Systolic blood pressure (SBP) greater than 150 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 95 or less than 50 mm Hg at screening or baseline. Measurements may be repeated at the investigator*s discretion.
6. Use of prohibited medications (e.g., anti-epileptic drugs).
7. Administration of a vaccine in general within 2 weeks before study drug administration, and 4 weeks anti-COVID vaccines with mRNA in particular.
8. Loss or donation of blood over 500 mL within 90 days (males) or 120 days (females) prior to screening or intention to donate blood or blood products during the study.
9. Unsatisfactory venous access.
10. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study) including not having previously been dosed with NX210c.
11. History of abuse of addictive substances (alcohol, illegal substances) in the past 5 years of screening or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent.
12. Positive test for alcohol and/or drugs of abuse at screening or baseline (urine drug screen or alcohol breath test). Measurements may be repeated at the investigator*s discretion.
13. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit. Former smokers of more than 10 cigarettes per day will be eligible, provided they have not smoked more than 10 cigarettes per day for at least 3 months prior to the dosing of study drug.
14. Any contra-indication to glucose 5% or allergy to any component of the formulation, including corn allergy.
15. For CSF sampling, any of the criteria below:
a. History of clinically significant hypersensitivity to local anesthetics that may be used for LP (e.g., lidocaine).

b. Criteria that would preclude an LP, such as a local infection at the site of the LP, <100 × 103/µl platelet count at screening or clinically significant coagulation abnormality or significant active bleeding, or treatment with an anticoagulant or treatment with more than two antiplatelet agents.
c. History of clinically significant back pathology and/or back injury (e.g., degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with LP.
16. Any contraindication to MRI and DCE-MRI scanning, such as implanted metal clips or wires of the type that may concentrate radiofrequency fields or cause tissue damage from twisting in a magnetic field (e.g., aneurysm clips), implanted neural stimulators, implanted cardiac pacemakers or auto defibrillators, cochlear implants, ocular foreign bodies (e.g., metal shavings), any implanted device (pumps, infusion devices, etc.), or shrapnel injuries. Any contraindication of gadolinium for DCE-MRI. Inability to undergo MRI according to the investigator*s opinion (e.g., unable to lay still for the duration of the MRI).
17. Positive screening cultures for Multidrug resistant bacteria (BRMO) and/or Methicillin resistant staphylococcus aureus (MRSA) or no consent to perform BRMO and MRSA culture in case of increased risk for colonization with these bacteria.

AD patients only:
18. Dementia due to any condition other than AD, including VaD.
19. Clinically significant neurological disease other than AD, including but not limited to epilepsy or anti-epileptic drug therapy, stroke within 6 months before screening, or concomitant with onset of dementia, significant neuroimaging abnormalities, previously known or discovered on screening brain MRI, concussion or other acute head trauma in the past six months.
20. Use of memantine within 21 days before first dose.

PaD patients only:
18. Other known or suspected cause of Parkinsonism other than idiopathic PaD, including but not limited to, progressive supranuclear gaze palsy, drug- or toxin-induced parkinsonism, essential tremor, primary dystonia, vascular parkinsonism.
19. Clinically significant neurological disease other than PaD, such as multi-infarct dementia, Huntington's disease, normal-pre

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:	Completed
Start date (anticipated):	09-12-2022
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NX210c
Generic name:	N.a.

Ethics review

Approved WMO Date:	25-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	22-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	01-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	12-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2023
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	EUCTR2022-002868-76-NL
CCMO	NL82392.056.22