A Phase 2a, Open-label, Multicenter Study to Evaluate Safety and Tolerability of Repeated Administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in Participants with Prodromal to Mild Alzheimer*s Disease

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The primary objective is to determine the safety, tolerability and preliminary efficacy of repeated intrathecal administration of NurOwn® (MSC-NTF: Autologous Mesenchymal Stem Cells [MSC] Secreting Neurotrophic Factors [NTF]) given three times at...

Ethical review	Not approved
Status	Will not start
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON49256

Source
ToetsingOnline

Brief title
BCT-201-EU

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Brainstorm Cell Therapeutics, Ltd.
Source(s) of monetary or material Support: Funded by Brainstorm Cell Therapeutics;Ltd.

Intervention

Keyword: AD, Alzheimer's Disease

Outcome measures

Primary outcome

The primary endpoint will be to evaluate the safety and tolerability of 3 intrathecal administrations of NurOwn® (MSC-NTF cells).

Safety endpoints include AEs, changes in physical and neurological examination findings, hematology, serum chemistry, urinalysis, vital signs, and requirement of concomitant medications.

Secondary outcome

Modulation of Cerebrospinal Fluid (CSF) and Blood Biomarkers

The efficacy of NurOwn® (MSC-NTF cells) will be evaluated by the modulation of CSF and blood biomarkers (neurotrophic factors, neurodegenerative and inflammatory biomarkers) following NurOwn® treatment.

CSF and blood samples will be collected as per the schedule of assessments to evaluate biomarkers (NTFs, inflammatory factors, cytokines and miRNAs) in the cerebrospinal fluid (CSF) before each treatment as well as in blood samples (such as Neurofilament Light Chain) throughout the study, to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells).

Cognitive Assessments

Change from baseline in all cognitive assessments will be summarized.

The assessments include Mini Mental State Examination (MMSE),

Neuropsychological Test Battery (NTB), Alzheimer's Disease Cooperative Study

Activities of Daily Living (ADCS-ADL) and Clinical Dementia Rating * Sum of

Boxes (CDR-SB).

Study description

Background summary

This is an open-label study with a single treatment arm involving 40 participants with Alzheimer*s Disease at multiple investigational study sites. After providing informed consent, participants meeting the inclusion and exclusion criteria will be enrolled and 1-4 weeks later will undergo a bone marrow aspiration (BMA). The first intrathecal (IT) administration will be at Visit 3 (Week 0), 6-10 weeks after screening/enrollment visit, with the subsequent treatments at Visit 4 (Week 8) and Visit 5 (Week 16). Following the third and last treatment, participants will be followed through a 12 week post treatment Visit 6 (Week 28) and a final follow-up to assess safety and disease progression at Visit 7 (Week 42).

Each subject*s participation in the study will last for approximately 52 weeks (12 months), consisting of:
* An approximate 10-week pretreatment period during which participants will undergo bone marrow aspiration and baseline evaluations
* A 16-week treatment period during which participants will be administered 3 treatments of NurOwn® (MSC-NTF cells) at 8-week intervals (Day 0-1, week 8, and week 16)
* A 12-week follow-up period (Week 28, Visit 6)
* A 14-week follow-up period to assess safety and clinical disease progression (Week 42, Visit 7)

Study drug will be supplied in one 5 mL syringe containing 4 mL of NurOwn® (MSC-NTF cells) suspension at a dose of 100-125 x106 cells for IT administration.

Study objective

The primary objective is to determine the safety, tolerability and preliminary efficacy of repeated intrathecal administration of NurOwn® (MSC-NTF: Autologous Mesenchymal Stem Cells [MSC] Secreting Neurotrophic Factors [NTF]) given three times at two monthly intervals to participants with prodromal to mild Alzheimer*s Disease.
The secondary objective is to evaluate the effect of NurOwn upon blood and CSF biomarkers and cognitive and clinical outcome measures, including Mini Mental State Examination (MMSE), Free and Cued Selective Reminding Test (FCSRT), Clinical Dementia Rating Scale * Sum of Boxes (CDR-SB), Neuropsychological Test Battery (NTB) subtests, Delis-Kaplan Executive Function System (D-KEFS), Category Fluency and Letter Fluency tests and Amsterdam Instructional Activities of Daily Living * Short Version (A-IADL-Q-SV), to measure safety and efficacy.

Study design

This is an open-label study with a single treatment arm involving 40 participants with Alzheimer*s Disease at multiple investigational study sites. After providing informed consent, participants meeting the inclusion and exclusion criteria will be enrolled and 1-4 weeks later will undergo a bone marrow aspiration (BMA). The first intrathecal (IT) administration will be at Visit 3 (Week 0), 6-10 weeks after screening/enrollment visit, with the subsequent treatments at Visit 4 (Week 8) and Visit 5 (Week 16). Following the third and last treatment, participants will be followed through a 12 week post treatment Visit 6 (Week 28) and a final follow-up to assess safety and disease progression at Visit 7 (Week 42).

Intervention

Doses of 100-125 x106 NurOwn® (MSC-NTF cells) administered intrathecally at visits 3, 4 and 5.

Study burden and risks

The study drug may have side effects. These side effects are common (occurs in 1 in 10 people or more):
* Headache
* Back pain
* Fever
* Pain in joint
* Injection Site Pain
* Constipation
* Pain in Extremity
* Neck Pain
* Nausea
* Cough

* Muscle pain

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
There may be unforeseen risks to an unborn child or breastfeeding infant associated with taking NurOwn® (MSC-NTF cells). The effect of MSC-NTF cells on an embryo or fetus, or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:
* Pregnant
* Trying to become pregnant
* Breastfeeding

Risk of Bone Marrow Aspiration
The most common and expected side-effects and discomforts reported when undergoing a bone marrow aspiration include the following:
* redness of the skin (erythema)
* swelling of the skin (induration)
* tenderness or pain at the site
* itching at the site
* infection
* fever
* damage to bone, nerve or muscle in hip region

Risks of Intrathecal Injection by Lumbar Puncture
A lumbar puncture is a routine procedure that will be used to administer the study drug and to collect CSF from the fluid filled space below the end of the spinal cord.
When spinal fluid is removed during a lumbar puncture, the risks include headache, bleeding and pain at the site where the needle was put in, and infection. Pain during the lumbar puncture procedure will be prevented or minimized by using local anesthesia (lidocaine). Infection after a lumbar puncture is very rare, but serious, and would be treated with antibiotics. Headache can occur if the lining around the spinal fluid (dura) is torn and some of the fluid leaks out. Post-lumbar puncture headaches are more common in females and in people less than 30 years old. This headache can be mild to severe. The patient may also have nausea, dizziness and ringing in the ears. Post-lumbar puncture headaches get worse when sitting or standing. Occasionally, the headache may be severe enough to interfere with normal daily activities.

Risks of Magnetic Resonance Imaging (MRI):
You will also have a Magnetic Resonance Imaging (MRI) brain scan at the beginning of the study to look at the changes in your brain which occur as a result of AD and which are thought to lead to the symptoms you may have. For the MRI scan you would need to lie down and keep still in the scanner for approximately 30 minutes. At one point in the procedure you would be given an injection with a solution called gadolinium so that the scanner can detect

particular changes in the brain. This solution is routinely used in MRIs. In addition, if you are a woman who can have children, a pregnancy test from a urine sample would be performed before each MRI scan to be sure you are not pregnant.

Risks of Cognitive Scales (MMSE, FCSRT, D-KES and NTB) and Questionnaires (A-ADL-Q-SV and CDR):
All of the assessments are widely accepted ways of assessing the status of patients with AD. Completing the cognitive scales/questionnaires may make the patient/caregiver feel uncomfortable, including emotional or mental discomfort. The patient/caregiver may refuse to answer any of the questions and may take a break at any time during the study.

Risks of Possible X-Ray-Guided Lumbar Puncture Procedure
If the doctor performing the administration of study drug is not able to safely access the spinal fluid, he or she may choose to have the procedure performed with the assistance of X-ray guidance.
If the doctor chooses to perform the procedure under X-ray guidance, the patient will be exposed to radiation.
The total amount of radiation exposure is equal to a whole-body exposure of about 2.9 milliSieverts (mSv).
A possible effect that could occur at doses used in this study is a slight increase in the risk of developing cancer later in life.

HIV Testing
As a part of this study, a sample of blood is being tested for the presence of HIV. If the blood test results are positive, the results of that test, and demographic information about the patient will be reported to the Department of Health as is required by law. In addition, this information will be available on the hospital*s laboratory reporting system.

Unknown Risks
There may be risks or side effects related to the study drug/device that are unknown at this time. The patient will be notified of any significant new findings that become known that may affect their willingness to continue in the study.

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. Males and females, ages 50 to 75 years old, inclusive, at the Screening Visit (Visit 1).
2. Clinical diagnosis of prodromal to mild AD at least 6 months prior to enrollment, based on the International Working Group (IWG-2) diagnostic criteria or the National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria.
3. Mini Mental State Examination (MMSE) of 20-30, inclusive, and Clinical dementia rating-global score (CDR-GS) of 0.5 or 1.0
4. Demonstrated abnormal memory function
5. CSF profile consistent with AD: Amyloid Beta 42 (A*42) concentration of <1000 pg/ml AND P-tau >19 pg/ml or ratio of p-tau/Abeta > 0.024 (Elecsys assay)
6. If currently treated with Cholinesterase Inhibitors (AChEI) (donepezil, galantamine, or rivastigmine) or Memantine the dose should be stable for at least 12 weeks prior to Screening (Visit 1).
7. Must have a caregiver that is willing to participate in the study and is able to provide accurate information on the participant's cognitive and functional ability.
8. Must consent to apolipoprotein E (ApoE) genotyping or willing to provide previous test results.

9. If sexually active and of childbearing potential, both females and males must agree to use an effective birth control method during the study and for at least 3 months following the last transplantation, such as: abstinence, intrauterine device (IUD), oral contraception, barrier and spermicide or hormonal implant.

Exclusion criteria

1. Prior stem cell therapy of any kind.
2. Active participation in any other interventional study or use of unapproved AD investigational therapy within 60 days prior to the Screening Visit (Visit 1), unless proven to have been on placebo.
3. Inability to lie flat for the duration of intrathecal cell administration and/or bone marrow aspiration, or inability to tolerate study procedures for any other reason.
4. History of clinically significant autoimmune disease (excluding thyroid disease) that may confound study results, myelodysplastic or myeloproliferative disorder, leukemia or lymphoma, whole body irradiation, hip fracture, or severe scoliosis.
5. Any poorly controlled clinically significant medical condition other than Alzheimer*s disease (e.g., within six months of Screening Visit (Visit 1), such as myocardial infarction, angina pectoris, congestive heart failure, or hypertension (repeated blood pressure >180 mmHg systolic or 100 mmHg diastolic) as well as clinically significant coagulopathy, treatment with anticoagulants that, in the opinion of the investigator, would compromise the safety of participants.
6. Any history of malignancy (e.g., myeloproliferative disorder, leukemia or lymphoma) within the previous 5 years, except for non-melanoma localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of Screening Visit (Visit 1)).
7. Any history of acquired or inherited immune deficiency syndrome.
8. Platelet count, INR, PT or PTT not within the normal range (local protocol) or other risk for increased or uncontrolled bleeding (safety for lumbar puncture and bone marrow).
9. Presence of contraindication to lumbar puncture as judged by local PI, e.g. need for anticoagulant or antiplatelet medications other than aspirin at a dose of * 100 mg/day or clopidogrel.
10. MRI evidence of a) more than three lacunar infarcts, b) territorial infarct or macroscopic hemorrhage, or c) deep white matter lesions (corresponding to a Fazekas score of 3).
11. Pregnant women or women currently breastfeeding.
12. Positive test result for Hepatitis B virus (HBV; surface antigen (HBsAg) and antibodies to core antigen (IgG and IgM anti-HBc)), Hepatitis C virus (HCV), Human Immune deficiency Virus (HIV) 1 and 2.
13. Any medical or neurological/neurodegenerative condition other than AD

(e.g.,vascular dementia, dementia with Lewy bodies, and Parkinson*s disease) that, in the opinion of the Investigator, might be a contributing cause to the participant's cognitive impairment or could lead to discontinuation, lack of compliance, interference with study assessments, or safety concerns (includes, low vitamin B12 level, low Hb level (<100); hypothyroid disease).
14. History within the past 6 months or evidence of clinically significant psychiatric illness (e.g., major depression, suicidality, schizophrenia, or bipolar affective disorder).
15. Any condition, which in the opinion of the investigator or the Sponsor makes the patient unsuitable for inclusion.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO

Date:	16-07-2020
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	01-09-2020
Application type:	First submission
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
EudraCT	EUCTR2020-002872-11-NL
CCMO	NL74415.000.20