A multicenter, randomized, active-controlled, double-blind, double-dummy, parallel group clinical trial, investigating the efficacy, safety, and tolerability of continuous subcutaneous ND0612 infusion in comparison to oral IR-LD/CD in subjects with Parkinson*s disease experiencing motor fluctuations (BouNDless)

Published: 13-01-2020
Last updated: 10-04-2024

Primary ObjectiveThe primary objective of the study is to determine the effect of ND0612 on daily *ON* time without troublesome dyskinesia (defined as the sum of "ON" time without dyskinesia and *ON* time with non-troublesome dyskinesia)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON52856

Source
ToetsingOnline

Brief title
BouNDless

Condition

- Movement disorders (incl parkinsonism)

Synonym
movement disease, Neurodegenerative movement disorder

Research involving
Human

Sponsors and support

Primary sponsor: Neuroderm Ltd.
Source(s) of monetary or material Support: industry

Intervention

Keyword: infusion, LD/CD solution, ND0612, Parkinson

Outcome measures

Primary outcome

DBDD Maintenance Period (DB W12) in the mean daily "ON" time without troublesome dyskinesia ("GOOD ON") adjusted to subject's waking hours and normalized to 16 waking hours, based on subject's "ON/OFF" diary assessments on the 3 consecutive days before the visit.

"GOOD ON" is defined as the sum of "ON" time without dyskinesia and "ON" time with non-troublesome dyskinesia.

Secondary outcome

The key secondary efficacy endpoint is the change from Baseline to the end of the DBDD Maintenance Period (DB W12) in the mean daily "OFF" time adjusted to subject's waking hours and normalized to 16 waking hours, based on subject's "ON/OFF" diary assessments on the 3 consecutive days before the visits.

Study description

Background summary

Parkinson*s disease (PD) is a neurodegenerative movement disorder characterized by tremor, bradykinesia, muscular rigidity, and gait impairment as a result of marked dopamine deficiency in the basal ganglia of the brain due to the loss of dopaminergic neurons. Dopamine itself does not cross the blood-brain barrier, but its metabolic precursor, levodopa (LD), can permeate into striatal tissue and has, therefore, been an important drug in the treatment of the disease. For the past 40 years, LD (or L-Dopa) has remained the most effective therapy for the treatment of PD.
Attempts are being made to provide more sustained dopamine concentrations in the central nervous system, known as continuous dopaminergic stimulation, by using novel LD preparations. The current available long-acting oral LD therapies failed to reduce the risk of motor complications in controlled trials. In contrast, long lasting and dramatic reductions in motor complications associated with reduced dyskinesias and *OFF* periods (phases with no response to medication and significant motor symptoms) have been observed in PD subjects when treated with continuous infusion of LD (intravenous or intraduodenal) or dopamine agonists. Unfortunately, the infusion approaches to date have inherent limitations in that they are neither convenient nor practical treatment options and dopamine agonists fail to reach the efficacy of LD and bear major adverse effects.
LD and CD have been used extensively in humans by the oral route. NeuroDerm, Ltd. (NeuroDerm) is developing an LD/CD solution for continuous subcutaneous (SC) administration via infusion pump system for the treatment of idiopathic PD. The LD/CD solution ND0612 contains 60 mg/mL LD and 7.5 mg/mL of CD. ND0612 is being developed for patients with LD-responsive PD who do not have satisfactory control of debilitating motor fluctuations and hyper/dyskinesia despite optimized treatment with commercially available PD products.
Non-clinical and clinical studies to date support the continued evaluation of ND0612 as a way to provide continuous and stable sources of LD for transport to the brain for the treatment of PD.

Study objective

Primary Objective
The primary objective of the study is to determine the effect of ND0612 on daily *ON* time without troublesome dyskinesia (defined as the sum of "ON" time without dyskinesia and *ON* time with non-troublesome dyskinesia) using subject-completed *ON/OFF* diary assessments of motor function in subjects with Parkinson*s disease (PD) experiencing motor fluctuations.

Secondary Objectives

Key secondary objective of the study is to determine the effect of ND0612 on daily *OFF* time in subjects with PD experiencing motor fluctuations using subject completed *ON/OFF* diary assessments of motor function.

Other secondary objectives are to determine the effect of ND0612 on:
• Movement Disorder Society-Unified Parkinson*s Disease Rating Scale (MDS-UPDRS) Part II (Motor Aspects of Experiences of Daily Living [M-EDL]).
• Patient Global Impression of Change (PGIC).
• Clinical Global Impression of Improvement (CGI-I).
• MDS-UPDRS Part III (Motor Examination), measured in the *OFF* state or approximately 15 minutes before the next encapsulated oral dose (LD/CD or placebo).
• Daily *ON* time without dyskinesia (troublesome or non-troublesome) using subject-completed *ON/OFF* diary assessments of motor function.
• Proportion of responders in *OFF* time.
• Parkinson*s disease Quality of Life (QoL) based on the 39-item PD Quality of Life questionnaire (PDQ-39).
• The Parkinson*s Disease Sleep Scale (PDSS).

Study design

This study is comprised of 6 periods:
(1) a Screening Period (1-4 weeks);
(2) an open-label oral IR-LD/CD Adjustment Period (6 weeks) composed of 4 weeks titration and 2 weeks of stable oral IR-LD/CD dose
(3) an open-label ND0612 Conversion Period (6 weeks) composed of 4 weeks titration and 2 weeks of stable ND0612 and oral IR-LD/CD dose.
(4) a randomized, double-blind, double-dummy, active-controlled Maintenance Period (12 weeks);
(5) an optional open-label Treatment Extension Period (1 year); and
(6) a Safety Follow-up Period (up to 4,5 years).
All subjects must have a named study partner (e.g., spouse, relative, friend, neighbor, or
caregiver) who is willing and able to support the subject during the study

Intervention

Subjects will be randomized in a 1:1 ratio at the Randomization visit (ND D42/DB D1) to 1 of 2 treatment groups:
• Test Group (Group A): ND0612 infusion + placebo IR-LD/CD (white) + active IR-LD/CD (grey)
• Control Group (Group B): IR-LD/CD (white) + placebo infusion + placebo IR-LD/CD (grey)

Study burden and risks

Patients are expected to:
-Complete questionnaires:
-Parkinson*s Disease Sleep Scale (5x)
-Quality of Life in Parkinson*s Disease (5x)
-EuroQol 5-dimensions, 5-levels Quality of Life Questionnaire (5x)
-keep a diary
-Provide urine samples (8x)
-have an ECG (5x)
-physical and neurological examination (5x)
-have blood draws 8x
- have subcutaneous placements of the infusion pump each day (with help of a study partner). Patient and partner will need to spend time training to learn how to operate the infusion pump. This will take at least 4 sessions with a minimum of 6 hours in total.

The patient will have approximately 22 scheduled visits to the hospital and 9 telephone visits. If patients choose to participate in the optional treatment extension period they will have an additional 20 hospital and 9 telephone visits during up to 4,5 years.

Continuous infusion of LD/CD with Duodopa/Duopa has proven efficacious in Phase 3 clinical trials and is marketed across the world. Duodopa/Duopa is administered directly to the jejunum via a PEG-J tube, and thus requires surgical intervention, and is associated with potentially serious surgical and gastrointestinal complications, including bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, perforation of the intestine or adjacent anatomical structures, pancreatitis, pneumoperitoneum and postoperative wound infection. Some of these adverse events have resulted in serious outcomes, including prolonged hospitalization, surgery and/or death.
ND0612 treatment is administered subcutaneously, therefore avoiding the side effects and burden of a surgical intervention. Data accumulated to date suggests that continuous ND0612 infusion is associated with a more benign safety profile that relates mainly to infusion site infections (cellulitis and abscess) that have been treated successfully with antibiotics and /or drainage and have resolved without any sequala, and transient local effects including subcutaneous nodules, infusion site erythema, edema, pain, and hematomas that resolve spontaneously.
Due to the above, the overall risk benefit balance for study ND0612-317 is considered to be favorable.

Contacts

Public

Neuroderm Ltd.

Ruhrberg Science building, Pekeris St. 3
Rehovot 7670212
IL
Scientific
Neuroderm Ltd.

Ruhrberg Science building, Pekeris St. 3
Rehovot 7670212
IL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female subjects with PD of any race at least 30 years of age who sign an Institutional Review Board/Ethics Committee-approved informed consent form (ICF).
2. Parkinson*s disease diagnosis consistent with the UK Brain Bank Criteria.
3. Modified Hoehn and Yahr scale in *ON* stage <= 3.
4. Subjects must experience motor fluctuations and experience an average of at least 2.5 hours daily (with a minimum of 2 hours every day) in the *OFF* state during the waking hours as confirmed by an adequately completed *ON/OFF* diary over 3 days.
5. Subject treatment should be at least 4 doses/day of LD/ Dopa Decarboxylase Inhibition (DDI) (or at least 3 doses/day of extended release LD/DDI, e.g., Rytary) and at least 400 mg/day of LD, or equivalent according to the conversion table, and, according to the Investigator*s judgement, the subject experiences motor fluctuations that cannot be further improved by adjusting anti-PD medications.
6. Subjects and/or study partners have no impediment that may prevent them from

operating the pump system.
7. Subjects and/or study partners must demonstrate ability to keep accurate diary entries of PD symptoms (*ON/OFF* diaries) with at least 75% concordance with the the Blinded Efficacy Rater by the end of the diary training session during the Screening Period, including at least 1 *OFF* assessment.
8. Mini Mental State Examination (MMSE) score >= 24.
9. Female subjects must be surgically sterile (hysterectomy, bilateral oophorectomy, or tubal ligation); postmenopausal (defined as cessation of menses for at least 1 year); or willing to practice a highly effective method of contraception. All female subjects must be non-lactating and not pregnant and have a negative urine pregnancy test at Screening and at Enrollment (IR1 D1). Female subjects of childbearing potential must practice a highly effective method of contraception (such methods include combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation: oral / intravaginal; transdermal / progestogen-only hormonal contraception associated with inhibition of ovulation: oral / injectable; implantable / intrauterine device [IUD] / intrauterine hormone-releasing system [IUS]/ bilateral tubal occlusion / vasectomized partner/ sexual abstinence) from 1 month before Enrollment (IR D1 /V2) until 1 month after the last dose of study treatment. Alternatively, true abstinence is acceptable when it is in line with the subject*s preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, the subject and sexual partner must comply with the contraceptive requirements detailed above.
10. Willingness and ability to comply with study requirements.
11. Subjects must have a named study partner that signed the ICF.
12. Approval for entry into the study by an independent EAC.

Exclusion criteria

1. Atypical or secondary Parkinsonism.
2. Acute psychosis or troublesome hallucinations in the past 6 months.
3. Subjects with clinically significant or unstable medical, surgical, or psychiatric condition or laboratory abnormalities which, in the opinion of the Investigator or the EAC, represents a safety risk, makes the subject unsuitable for study entry, or potentially unable to complete all aspects of the study.
4. Clinically significant ECG abnormalities.
5. Renal or liver dysfunction that may alter drug metabolism including Screening Visit serum levels of creatinine > 1.5 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 × upper limit of normal, and total bilirubin > 2.5 mg/dL.
6. Any malignancy in the 5 years before enrollment, except basal cell carcinoma of the skin, squamous cell carcinoma in situ, or cervical carcinoma in situ that have been successfully treated.
7. Use of subcutaneous (SC) apomorphine injections, sublingual apomorphine, or inhaled LD within 4 weeks before the enrollment.

8. Concomitant therapy or within 28 days before enrollment with: metoclopramide, reserpine, methylphenidate, or amphetamines, well as neuroleptics; exception in case of Quetiapine and Pimavanserin use: (1) allowed only in case it had been used for a period of at least 3 months before enrollment, (2) subject is on stable therapy for at least 3 months (3) underlying psychosis to be under control and anticipating no changes to the dosage of the medication throughout the study.
9. Subjects with a history of alcohol or substance abuse within the past 12 months.
10. Subjects who have taken experimental medications within 30 days before enrollment.
11. Subjects who have previously participated in studies ND0612H-006 and/or ND0612H-012.
12. Subjects who have previously undergone treatment for PD with a surgical intervention (e.g., pallidotomy, thalamotomy, transplantation, deep brain stimulation procedures), gene therapy, Duodopa®/Duopa®, or continuous dopaminergic or apomorphine infusion. Subjects who have discontinued Duodopa®/ Duopa® treatment at least 6 months before enrollment and have undergone stoma closure surgery at least 6 months before enrollment, may be included in this study. Subjects who are planning to undergo treatment for PD with a surgical intervention will be enrolled at the Investigator*s discretion.
13. Subjects with severe disabling dyskinesias, based on Investigator's discretion.
14. History of significant skin conditions or disorders (e.g., psoriasis, atopic dermatitis, etc.) or evidence of different lesions (e.g., sunburn, acne, scar tissue, tattoo, open wound, branding, or pigmentation) that, in the Investigator's opinion, would interfere with the infusion of the study drug or could interfere with study assessments.
15. Subjects who do not have sufficient SC tissue for SC infusion treatment.
16. Use of non-selective monoamine oxidase inhibitors (e.g., phenelzine, isocarboxazid, tranylcypromine) within 4 weeks before enrollment.
17. Use of monoamine-depleting agents (e.g., reserpine, tetrabenazine, deutetrabenazine, valbenazine, xenazine) within 4 weeks before enrollment.
18. Current or previous diagnosis of Dopamine Dysregulation Syndrome or Impulse Control Disorder.
19. Impulse control disorder within the past 2 years, if considered clinically significant by the investigator.
20. Subjects who answered "yes" to questions 4 or 5 of the C-SSRS within the last 5 years.
21. Known allergy to the study drug or placebo or any of their excipients.
22. Subjects with narrow angle glaucoma

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:	Recruiting
Start date (anticipated):	05-11-2020
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carbidopa and Levodopa tablets
Generic name:	Carbidopa and Levodopa tablets
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	levodopa/carbidopa
Generic name:	levodopa/carbidopa

Ethics review

Approved WMO Date:	13-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2020
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-004156-37-NL
CCMO	NL71718.018.19