A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of NBI-827104 in Subjects with Essential Tremor.

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- To evaluate efficacy of NBI-827104 in subjects with ET - To evaluate safety and tolerability of NBI-827104 in subjects with ET- To evaluate pharmacokinetics of NBI-827104 and metabolite (if quantified) for each treatment in subjects with ET

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

Summary

ID

NL-OMON51977

Source
ToetsingOnline

Brief title
Safety and efficacy of NBI-827104 in essential tremor

Condition

- Movement disorders (incl parkinsonism)

Synonym
Essential Tremor, ET

Research involving

Human

Sponsors and support

Primary sponsor: Neurocrine Biosciences
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Calcium channel blocker, Essential tremor, Tremolytic activity

Outcome measures

Primary outcome

* Change from baseline in amplitude at peak frequency (mg2/Hz) of postural

tremor (extended hand position) in the more severely affected hand1 measured

using laboratory tremography at the last day of each treatment period

* Incidence of:

o Adverse Events (AEs)

o Suicidality measured by Columbia Suicide Severity Rating Scale (C-SSRS)

* Absolute values and changes from baseline values in:

o clinical laboratory tests (haematology, chemistry)

o vital signs

o 12-lead ECGs

Secondary outcome

* Change from baseline by timepoint in the following:

* The Essential Tremor Rating Assessment Scale (TETRAS) Performance score

(independent blinded video rating)

* TETRAS ADL score

* Clinical Global Impression of Change (CGI-C).

* PK parameters for NBI-827104 and metabolites will be determined by standard

non-compartmental analysis of the plasma concentration-time data, including but

not limited to:

o AUCtau, CL/F, Cmax, Ctrough, lambdaz, t1/2, tmax

o Dose-normalized PK parameters: AUCtau, Cmax, Ctrough

Study description

Background summary

Essential tremor (ET) is one of the most common movement disorders, affecting approximately 5% of adults aged 65 years or older. ET is considered a tremor syndrome characterized by bilateral upper-limb action tremor, defined as tremor occurring during muscle activity resulting in kinetic and/or postural tremor. While tremor of the upper limbs is considered the cardinal symptom, additional body parts can be affected by tremor, including the head, voice, and legs. T-type calcium channels were identified as having a critical physiological and pathological role in diseases or disorders such as ET, where abnormal oscillatory activity occurs in the brain. They are expressed in several areas of the network associated with tremor, particularly in neurons of the inferior olive but also in Purkinje cells and neurons of the deep cerebellar nuclei. The causal connection between T-type calcium channels and ET is based primarily on studies using harmaline, a beta carboline derivate known to induce action tremor of 8 to 12 Hz frequency in various species.

NBI-827104, a novel selective and orally available T-type calcium channel blocker, is a potent inhibitor of the 3 T-type voltage-gated calcium channel (Cav) subtypes Cav3.1, 3.2, and 3.3, and has demonstrated tremolytic activity in 2 rodent models of action tremor, including the harmaline-induced rat model of ET. NBI-827104 has been well tolerated in clinical studies in healthy adult subjects at single doses up to 400 mg(7) and multiple doses up to 100 mg QD following titration. Based on the mechanism of action, activity in nonclinical models of action tremor, and clinical safety profile, NBI-827104 is being evaluated for treatment of ET in adult subjects in this phase 2 clinical study.

Study objective

- To evaluate efficacy of NBI-827104 in subjects with ET
- To evaluate safety and tolerability of NBI-827104 in subjects with ET
- To evaluate pharmacokinetics of NBI-827104 and metabolite (if quantified) for each treatment in subjects with ET

Study design

This is a phase 2, randomized, double-blind, placebo-controlled, 2 treatment period crossover study with up-titrated dosing to evaluate the safety, tolerability, PK and efficacy of oral NBI-827104 QD dosing in subjects with ET

Intervention

Placebo and NBI 827104 for 28 days (cross-over), with an up-titration regimen for NBI 827104with weekly increases (10, 30, 60 and 100 mg)

Study burden and risks

The study population of male and female subjects 18 to 75 years of age is appropriate based on the characteristic onset of ET during adult life and nearly full penetrance of ET before the age of 65. Both male and female subjects are included, as there is no evidence for predominance for ET in males or females. In short, the risks to individuals enrolled to this trial have been minimised by using an up-titration scheme. The decision to escalated to the next dose level will be based upon individual safety assessments. We will also be specifically monitoring target organs of toxicity based upon (pre)clinical data * namely the eye lens, thyroid and central nervous system. The potential benefits apply to patients with essential tremor, so they have the opportunity to receive an investigational drug which more effectively relieves their tremor with less side-effects than current standard treatment (e.g. propranolol and primidone).

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. Signed informed consent prior to any study-mandated procedure.
2. Male or female subjects, 18 to 75 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 35 kg/m2, inclusive, at screening.
4. Diagnosis of Essential Tremor (inclusive of Essential Tremor plus) as defined by the Movement Disorders Society Consensus Criteria for Tremor.
5. Confirmation of bilateral upper limb action tremor in the absence of overt dystonia, ataxia, or parkinsonism by an independent rating based on the video recorded at screening of the standardized exam following the TETRAS Performance Subscale.
6. History of onset of tremor before 65 years of age.
7. Tremor Performance score of *2 on at least 2 of the 6 upper limb manoeuvres (Item 4) on the TETRAS Performance Subscale and a total TETRAS Performance score *15 at screening (investigator and independent video rating).
8. All women of childbearing potential and all males must practice effective contraception (as defined in section 4.5.1 of the protocol) during the study and be willing and able to continue contraception for at least 90 days after their last dose of study drug.
9. Has the ability to communicate well with the Investigator in the Dutch or English language and is willing to comply with the study procedures and restrictions.

Exclusion criteria

1. Evidence of any acute (at screening or prior to first dose) or chronic

disease or condition that could interfere with, or for which the treatment 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 rate, body temperature] and 12-lead ECG). For example, neurological conditions other than ET [plus] like cognitive impairment or myasthenia gravis, uncontrolled psychiatric disorders or malignancy. Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
2. Have direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor.
3. Have known history of other medical or neurological conditions that may cause or explain subject's tremor, including, but not limited to: Parkinson's disease, dystonia, cerebellar disease other than ET, traumatic brain injury, alcohol abuse or withdrawal, mercury poisoning, hyperthyroidism, pheochromocytoma, head trauma or cerebrovascular disease (within 3 months prior to the onset of ET), multiple sclerosis, and family history of Fragile X syndrome.
4. Have had prior magnetic resonance guided focused ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy).
5. Clinically significant impaired balance or at increased risk for falls, including the inability to ambulate safely unaided.
11. Are currently taking any of the prohibitive medications listed in Appendix 2. Subjects who have received these medications in the past, must have been off them for at least 30 days prior to first dose. Stable dosage of 1 other anti-tremor medication, excluding primidone, is allowed from 30 days before screening if anticipated to be stable from screening until end of study. If on primidone, subjects are allowed to extend the screening period by 2 weeks (for a total of 6 weeks) and discontinue primidone under the supervision of the investigator.
22. Have a significant risk of suicidal or violent behaviour. Subjects will be excluded if they have:
* Any lifetime history of suicidal behaviour or
* Any lifetime history of suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2021
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NBI-827104
Generic name:	NBI-827104

Ethics review

Approved WMO Date:	10-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	06-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	18-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-05-2022
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	EUCTR2020-006012-24-NL
CCMO	NL76780.056.21