Safety, pharmacokinetics and pharmacodynamic effects of NMD670

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25316

Source
NTR

Brief title
CHDR1948

Health condition

Myasthenia Gravis

Sponsors and support

Primary sponsor: NMD Pharma A/S
Source(s) of monetary or material Support: NMD Pharma A/S

Intervention

Outcome measures

Primary outcome

Tolerability / safety endpoints
The following endpoints will be determined at time points indicated in the Schedule of Assessments.
• Serious adverse events (SAEs) and adverse events (AEs) will be collected throughout the study at every study visit.

• Concomitant medication
• Clinical laboratory tests
o Haematology
o Chemistry
o Urinalysis
o Coagulation
• Vital signs
o Pulse Rate (bpm)
o Systolic blood pressure (mmHg)
o Diastolic blood pressure (mmHg)
o Respiratory rate
• ECG
o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF
• 24-hour Holter recording
• Handgrip dynamometry
o Grip release profile; timeprofile from 100% maximum voluntary contraction (MVC) to 5% of the 100%MVC
o 100%MVC (Part C only)

Secondary outcome

Pharmacokinetic endpoints
Blood and urine samples for assay of NMD670 and its metabolite will be taken at timepoints indicated in the Visit and
Assessment Schedule.
• PK endpoints for single dose cohorts: Cmax, tmax, AUClast, AUCinf, AUC extrapolated, t½, Lambda_z, CL/F, and Vz/Fof NMD670.
Cmax/D, AUCinf/D.
• PK endpoints for multiple dose cohorts: AUCtau, AUCinf (after first dose), Cmax, Cmin, tmax t½, Lambda_z, CL/F, Vz/F, MRTT and MRT∞ (after the first dose); Ctrough on intervening days (see Visit and Assessment schedule) and the last day of dosing; Rac(Cmax)
and Rac(AUC) of NMD670. Cmax/D and AUCtau/D after the first and the last dose.
• Metabolite Evaluation plasma: Tmax, AUC
• Metabolite evaluation urine: Aelast, Aelast%, CLR.

Study description

Background summary

Myasthenia gravis is an auto-immune disease, caused by antibodies against the acetylcholine receptor (AChR) or other molecular
structures on the post-synaptic side of the neuromuscular junction in skeletal muscle fibres. Loss of AChR results in reduced strength of
neuromuscular transmission that can lead to failing muscle fibre activation and eventually

muscle weakness and excessive fatigability.
There is a need for safe and efficacious therapies to improve muscle function in these patients, in view of because of the side effects caused by
existing therapies, consisting of peripheral acetylcholinesterase inhibitors and immunosuppressive drugs. At the neuromuscular junction, the transmission of the nerve action potential to the muscle membrane involves flow of both excitatory and inhibitory currents. Excitation of muscle requires that the excitatory current outweighs inhibitory current flow. In myasthenia gravis the excitatory current flow is reduced due to the loss of functional AChR. Skeletal muscle specific ClC-1 chloride ion channels carry the inhibitory currents that counteract neuromuscular transmission. Inhibition of ClC-1 reduces the inhibitory current and thereby increases muscle membrane excitability and strengthens neuromuscular transmission. This was shown to lead to recovery of muscle function in nonclinical models of several neuromuscular diseases (Pedersen, Riisager, de Paoli, Chen, & Nielsen, 2016a).
NMD670 is a selective negative modulator of the ClC-1 channel, that is being developed as an oral treatment to improve motor function and improve quality of life in patients with myasthenia gravis, and possibly other diseases that lead to dysfunction of neuromuscular transmission.

Study objective

• To assess safety and tolerability of single oral doses of NMD670 in healthy male and female subjects
• To assess safety and tolerability of repeated oral doses of NMD670 in healthy male subjects
• To assess safety and tolerability of single oral doses of NMD670 in patients with myasthenia gravis

Study design

-42 Days till EOS

Intervention

NMD670

Contacts

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Eligibility criteria

Inclusion criteria

Main inclusion criteria healthy volunteers (Part A and B)
1. Signed informed consent prior to any study-mandated procedure
2. Part A1: Healthy male subjects, 18 to 45 years of age, inclusive at screening.
3. Part A2: Healthy female subjects of non-childbearing potential, 18-65 years of age, inclusive at screening.
4. Part B: Healthy male subjects 18-65 years of age, inclusive at screening.
5. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
6. All males must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
7. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Main inclusion criteria myasthenia gravis patients (Part C)
1. Signed informed consent prior to any study-mandated procedure
2. Male and female subjects, 18 and above years of age, inclusive at screening.
3. Diagnosis of generalized myasthenia gravis, MGFA class II, III or IVa, based on characteristic muscle weakness and a positive AChR antibody test.
4. Patients using steroids should be using a stable dose of steroids for at least 1 month before screening, and the dose of steroids should be expected to remain stable for two months following screening.
5. Body mass index (BMI) between 18 and 34 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
6. All women of child bearing potential and all males must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
7. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.
8. Must be able to cease the use of pyridostigmine as per study requirements, if applicable.

Exclusion criteria

Main exclusion criteria healthy volunteers (Part A and B)
1. Evidence of 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 rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). 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 for healthy subjects.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening.
5. Abnormal findings in the resting ECG at screening defined as:
a. QTcF> 450 or < 300 msec for men and QTcF> 470 or < 300 msec for women
b. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm)
c. Personal or family history of congenital long QT syndrome or sudden death;
d. ECG with QRS and/or T wave judged to be unfavourable for a consistently accurate QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
e. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
8. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study).
9. History of abuse of addictive substances (alcohol, illegal substances) 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.
10. Positive test for drugs of abuse at screening or pre-dose. Retesting is allowed at the discretion of the Investigator.
11. Alcohol will not be allowed from at least 24 hours before screening or pre-dose.
12. 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.
13. Subjects will not be allowed to have excessive caffeine consumption, defined as >800 mg per day.
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.

16. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
17. History of trauma to the lower extremities or other conditions (most importantly neurological or muscle diseases) that, in the opinion of the investigator, could affect the electrophysiological measurements.
18. Excessive exercise within 7 days before study drug administration.
19. Clinically significant abnormalities in coagulation.

Main exclusion criteria myasthenia gravis patients (Part C)
1. Evidence of any active or chronic disease or condition apart from myasthenia gravis, 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 rate, body temperature) and 12-lead electrocardiogram (ECG)). Deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). 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.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Clinically significant abnormal findings in the resting ECG at screening, personal or family history of congenital long QT syndrome or sudden death, evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
5. Use of any medications that could influence the safety and conductance of the study (see prohibited concomitant medication) within 14 days of study drug administration, or less than 5 half-lives (whichever is longer).
6. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
7. Participation in an investigational drug study (last dosing of previous study was within 90 days prior to first dosing of this study).
8. History of abuse of addictive substances (alcohol, illegal substances) 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
9. Positive test for drugs of abuse at screening or pre-dose (unless the test is positive for prescribed drugs). Retesting is allowed at the discretion of the Investigator.
10. Alcohol will not be allowed from at least 24 hours pre-dose.
11. Any confirmed severe allergic reactions against any drug, or multiple drug allergies (nonactive hay fever is acceptable).
12. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.
13. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or relevant psychiatric disease (as judged by the Investigator).

14. History of trauma to the lower extremities or other conditions (most importantly neurological or muscle diseases) that, in the opinion of the investigator, could affect the electrophysiological measurements.
15. Clinically significant abnormalities in coagulation.
16. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
17. Gout or clinically relevant elevations in uric acid.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2020
Enrollment:	79
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N.A.

Ethics review

Positive opinion

Date:	04-06-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 54930
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8692
CCMO	NL73152.056.20
OMON	NL-OMON54930

Study results

Summary results
N.A.