Randomized, double-blind, placebo-controlled, multiple dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of YTX-7739, a novel oral inhibitor of Stearoyl-CoA-desaturases, in healthy volunteers and patients with Parkinson*s disease

Published: 13-08-2020
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To investigate the safety, tolerability and pharmacokinetics after multiple daily doses of YTX-7739

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

Summary

ID

NL-OMON55131

Source
ToetsingOnline

Brief title
Multiple dose study of YTX-7739

Condition

- Movement disorders (incl parkinsonism)

Synonym

Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Yumanity Therapeutics
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Parkinson's Disease, Pharmacodynamics, Pharmacokinetics, StearylCoA desaturase

Outcome measures

Primary outcome

- Safety:

o Safety and tolerability of YTX-7739 will be measured by assessing the

severity and incidence of treatment-emergent adverse events (TEAEs), clinical

laboratory tests, ECGs, vital signs and physical examinations.

- Pharmacokinetic:

o The non-compartmental PK parameters of YTX-7739 will be estimated including

AUC, C(max), T(max), elimination half-life (t1/2) and elimination rate constant

(Ke).

Secondary outcome

NA

Study description

Background summary

There are currently no disease-modifying drugs available for the major age-related neurodegenerative diseases, including Parkinson*s disease (PD). The lack of therapies results from a poor understanding of disease biology, unproven predictive value of animal models, challenges in translating pharmacology from animals to man and difficulties in patient stratification and assessment of clinical response. These challenges are exacerbated by a lack of novel drug targets and drug molecules. Yumanity Therapeutics uses a proprietary discovery platform that seeks to identify novel drug targets and drug molecules that protect cells from toxicity caused by the accumulation of misfolded proteins. Using this platform, the Yumanity team determined that elevated cellular levels of monounsaturated fatty acids regulates toxicity caused by alpha-synuclein, the major protein component of Lewy body pathology and a key genetic risk factor for Parkinson*s disease. In a variety of cellular assay systems, inhibitors of the enzyme stearoyl-CoA-desaturase (SCD) reduce levels of monounsaturated fatty acids and also reduce alpha-synuclein toxicity. YTX-7739 is a novel, orally active inhibitor of SCD enzymatic activity, showing preferential inhibition of the brain-predominant SCD5 isoenzyme (IC50 ~10nM) and lower potency at the systemically distributed SCD1 isozyme (IC50 ~600nM). Inhibition of SCD5 and SCD1 reduce levels of monounsaturated 16-Carbon and 18-Carbon fatty acids and reduce alpha-synuclein toxicity. Here, we aim to explore the safety, tolerability and pharmacokinetic properties of YTX-7739, as well as the pharmacodynamic response to YTX-7739, following 14-28 daily doses in healthy adult volunteers and individuals with Parkinson*s Disease.

Study objective

To investigate the safety, tolerability and pharmacokinetics after multiple daily doses of YTX-7739

Study design

This will be a randomized, double-blind, placebo-controlled multiple ascending dose (MAD) study in healthy volunteers (Part A) and Parkinson*s Patients (Part B).

Intervention

Part A:Cohort 1 : 25 mg OD YTX-7739 / matching placebo. The dose of cohort 2 and part B will be based on emerging data from cohort 1. Cohort A2 and cohorts in part B will be dosed for 28 days. The maximum dose is 400 mg.

Study burden and risks

The safety, tolerability, pharmacology and food effect of single doses of up to 400 mg YTX-7739 has been studied in humans in the SAD study. YTX-7739 was safe and well tolerated with few adverse events. All adverse events were mild or

moderate, of short duration and self-limiting. There were no serious or unexpected adverse events. In this context the risk associated with exposure after a single dose (taking into account the half-life of 30-91 hours in a fed state) to YTX-7739 is considered acceptable. The safety profile observed after single doses does not raise concerns for the multiple dose study. The target exposures for the multiple dose study are well below the highest exposures achieved in the SAD study, only the extent of exposure will be longer.

A potential risk is that the frequency and severity of adverse events may increase after multiple dosing compared to a single dose. Key pharmacokinetic findings from the SAD study have been taken into consideration in designing the current MAD study in order to mitigate this risk.
The AEs that are expected to occur include eye dryness/irritation, skin dryness and hair loss, all of which can be monitored well in the clinic. As discussed in the Investigator*s Brochure, the AEs in the pre-clinical studies were mild and reversible at the exposure levels that are targeted in this multiple dose study.

A concern prior to the SAD study was a mild, transient prolongation (maximal increase up to 27 msec,) in QTc observed in beagle dogs, that was not associated with arrhythmia. This concern has been addressed by the Holter ECG monitoring and concentration-QTcF modelling, which showed the upper CI of the QTcF reaching the 10 ms threshold at a concentration of 2160 ng/mL. In the multiple dose study, concentrations are targeted to stay around 800 ng/mL, which is well below this threshold.

Subjects will undergo regular blood draws, meibum expressions and several lumbar punctures during the study. Subjects in part A will eat a high-fat (standard breakfast for part B) meal daily for the duration of the dosing period. Ingredients for the breakfasts will be made available to the subjects by CHDR. Variations on the high-fat meal composition will be available.

No benefit is expected for participants.

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

Part A
1. Adult male or female subjects 18-55 years of age, inclusive.
Part B
2. Male or female subjects 40-75 years of age, inclusive, with a confirmed diagnosis of Parkinson*s disease (Hoehn and Yahr grade 1-3).
Part A + B
3. Healthy status as defined by absence of evidence of any significant active acute or chronic disease or illness following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry and urinalysis, as judged by the investigator;
4. Body mass index (BMI) between 18-32 kg/m2, inclusive, and with a minimum weight of 50kg and maximum weight of 120kg
5. If subject is a female, she agrees to report onset and duration of menses if it occurs anytime during participation in the study (screening to end of study)
6. Evidence of a personally signed and witnessed informed consent document indicating that the subject has been informed of all pertinent aspects of the study;

Exclusion criteria

Part A:
1. Clinically significant findings as determined by medical history taking, physical examination, fundoscopy, ECG, laboratory findings (abnormal lipid or

hormone profile) and vital signs;
2. Hemodynamic status at screening: systolic blood pressure <100 or >160 mmHg, diastolic blood pressure <50 or >95 mmHg, heart rate <45 or >100 bpm measured;

Part B:
3. Clinically significant findings as determined by medical history taking, MRI (Part B, cohort 4 only), physical examination, fundoscopy, ECG and vital signs, other than Parkinson*s disease;
4. Any current, clinically significant, known medical condition other than Parkinson*s disease. Patients with a diagnosis of neurological diseases, other than Parkinson*s disease, including Alzheimer*s disease, Huntington*s disease, vascular dementia, progressive supranuclear gaze palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, primary dystonia, epilepsy, etc., that are considered clinically relevant by the investigator.
5. Dementia indicated by MMSE <18 at Screening;
6. Use of drugs known to prolong QT interval;
7. Hemodynamic status at screening: results that are considered clinically relevant by the investigator;
8. Part B, cohort 4 only: any contra-indication to performing a MRI (including (an history of) a cardiac pacemaker, implanted cardiac defibrillator, neurostimulator, hydrocephalus pomp, drug pump, stents or clips in vessels, non-removable hearing aid, non-removable implants containing a magnet in the jaw, tissue expander in the breast, IUD, metal splinters of fragments in the body, non-removable medication patch, tattoo or permanent make-up applied less than 6 weeks ago, non-removable piercing, non-removable hair extensions containing metal);
9. An history of claustrophobia, tinnitus or hyperacusis;
10. Part B, cohor t4 only: an history of allergic reaction during previous MRI examination;
11. History of repeated head injury; history of epilepsy or seizure disorder other than febrile seizures as a child
12. Reside in a nursing home or assisted care facility
13. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study or interfere with the participant's ability to comply with study procedures or abide by study restrictions, or with the ability to interpret safety data
14. Prior lack of response to dopaminergic medication (for example, levodopa or a dopaminergic agonist)
15. Ccontinuous use of any of the following within 30 days prior to baseline: antipsychotics (including clozapine and olanzapine), metoclopramide, alpha methyldopa, clozapine, olanzapine, flunarizine, amoxapine, amphetamine derivatives, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, and modafinil. Single use up to 7 days prior to the start of the study is allowed for metoclopramide.

for all exclusion criteria please see protocol section 4.3, pages 51-53

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:	Recruitment stopped
Start date (anticipated):	04-09-2020
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	YTX-7739
Generic name:	Nvt.

Ethics review

Approved WMO Date:	13-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2020

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	09-11-2021
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

ID: 20317
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000034-17-NL
CCMO	NL72549.056.20
OMON	NL-OMON20317