Randomized, double-blind, placebo-controlled single ascending dose study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and food-effects of YTX-7739, a novel oral inhibitor of Stearoyl-CoA-desaturases, in healthy volunteers

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* Part A: To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of increasing doses of YTX-7739 in healthy subjects. * Part B: To study the effect of food on pharmacokinetics of YTX-7739 in a selection of subjects who...

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

Summary

ID

NL-OMON49863

Source
ToetsingOnline

Brief title
SAD and food-effect 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: Food-effect, Parkinson's Disease, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

Considering the exploratory nature of this study, the primary endpoints will be

the incidence and severity or AEs or treatment emergent AEs.

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 (namely oleic acid (C18:1n9) and palmitoleic acid (C16:1n7)) regulates toxicity caused by *-synuclein, the major protein component of Lewy body pathology and a key genetic risk factor for Parkinson*s disease. Oleic and palmitoleic acids are obtained through diet and also endogenously produced by the endoplamatic reticulum resident enzyme, stearoyl-CoA-desaturase (SCD). In a variety of cellular assay systems, SCD

inhibitors reduce levels of monounsaturated fatty acids and also reduce *-synuclein toxicity. This inhibition of SCD activity in brain, plasma, skin and other tissues can be quantified as the fatty acid desaturation index (FA-DI), which is the ratio of unsaturated to saturated fatty acids in a given tissue. YTX-7739 is a novel, orally active inhibitor of SCD enzymatic activity, showing inhibition of the brain-predominant SCD5 isoenzyme and the widely distributed SCD1 isozyme. Inhibition of SCD5 and SCD1 reduce levels of monounsaturated 16-Carbon and 18-Carbon fatty acids and reduce *-synuclein toxicity (Vincent, Tardiff et al. (2018); Fanning et al., (2018).
Here, we aim to explore the safety, tolerability, pharmacokinetic and pharmacodynamic properties of YTX-7739 in healthy adult volunteers (part A) as a prelude to further study this molecule as a potential disease modifying therapy for Parkinson*s disease and related neurological disorders. In part B, we aim to assess the effect of food on the pharmacokinetics of YTX-7739. In part C, we aim to explore the pharmacokinetics of low doses of YTX-7739 after administration in a fed state. Part C is being performed based on preliminary results of parts A and B.

Study objective

* Part A: To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of increasing doses of YTX-7739 in healthy subjects.
* Part B: To study the effect of food on pharmacokinetics of YTX-7739 in a selection of subjects who participated in the SAD study.
* Part C: To study the pharmacokinetics of low doses of YTX-7739 after administration in a fed state in healthy subjects

Study design

This study will comprise threefour parts. Part A will be a randomized, double-blind, placebo-controlled single ascending dose (SAD) in 40 to 48 healthy adults using a parallel design. Part B will be a food-effect study in which the subjects from the two highest dose cohorts of part A will be administered YTX-7739 on a second occasion. Part C will be an open label, all active treatment study of pharmacokinetics of low doses of YTX-7739 in a fed state.

Intervention

5mg, 10mg, 20mg, 30mg, 100mg, 250mg, 400mg or placebo

Study burden and risks

The proposed study involves exposure of healthy human volunteers to single oral doses of YTX-7739, an experimental drug that inhibits the enzyme stearoyl-CoA-desaturase. As discussed in the Investigators Brochure, single

oral doses of YTX-7739 were very well tolerated in animals. The primary concern requiring additional precautions was a mild, transient prolongation (maximal increase 26 msec) in QTc. QTc interval prolongation was most evident at the highest dose of 120 mg/kg/day in dogs, which had associated exposures of 10160 ng/mL (Cmax) and 167500 ng*hr/mL (AUClast). In animals, this mild effect of prolonging QTc was not associated with arrhythmia.The risks to the safety posed by administration of single oral doses of YTX-7739 are small and will be mitigated by inclusion of sentinel subjects in the first dosing cohort, initiation of dosing at a dose level expected to result in plasma concentrations of YTX-7739 greater than 10X below the concentrations that may produce an effect on QTc or any other known safety concern, holter monitoring and incorporation of careful safety and tolerability review prior to each dose escalation. As both parts include healthy volunteers, no benefit is expected.

Healthy subjects in the current study fall in a low risk category for complications of COVID-19, the disease caused by the SARS-CoV-2 virus. To prevent SARS-CoV-2 infections among trial participants, measures and procedures based on the advice issued by the Dutch Centre for Infectious Disease Control (RIVM) and COVID-19 measures declared by the Dutch government will be adhered to as outlined in CHDR SOP GGECOVID. Site trial staff in direct contact and/or within 1.5 m distance of study subjects will receive additional protection via the use of Personal Protective Equipment (PPE) and disinfectants. All trial subjects will be screened for SARS-CoV-2 with a PCR: 1) prior to the admission at the clinical unit; 2) in case of symptoms possibly related to COVID-19. Healthy subjects will be excluded from the study when tested positive for SARS-CoV-2.

Based on the mechanism of action of YTX-7739 and the available information in the Investigators Brochure, there is currently no reason to believe that the investigational drug could 1) increase the susceptibility of trial participants to the SARS-CoV-2 virus, or 2) worsen or mask any COVID-19 signs, symptoms or complications. Pre-clinical data does not show evidence of any immunocompromising or respiratory effects. The clinical safety data from parts A and B of this trial shows no YTX-7739 related abnormalities in hematology, vital signs and physical examination. Overall, a single dose of YTX-7739 was well tolerated and adverse events occurred with comparable frequency in subjects receiving YTX-7739 and in subjects receiving placebo. The doses planned for part C of the study are 20 to 40 times lower than the highest dose administered in parts A and B.

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. Healthy male and female subjects 18-45 years of age, inclusive. Healthy status is defined by absence of evidence of any 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, coagulation and urinalysis;
2. Body mass index (BMI) between 18-35 kg/m2, inclusive, and with a minimum weight of 50kg and maximum weight of 120kg;
3. Evidence of a personally signed, dated and witnessed informed consent document indicating that the subject has been informed of all pertinent aspects of the study;
4. Able and willing to give written informed consent and to comply with all study restrictions.

Exclusion criteria

1. Legal incapacity or inability to understand or comply with the requirements of the study;

2. Clinically significant findings, as judged by the investigator, as determined by medical history taking, physical examination, ECG and vital signs;
3. Subjects with a borderline QTcF of > 450 ms for males and > 470 ms for females at screening or a history of long QT syndrome;
4. Hemodynamic status at screening: systolic blood pressure <100 or >160 mmHg, diastolic blood pressure <60 or >95 mmHg or heart rate <45 or >100 bpm
5. Any current, clinically significant, known medical condition, as judged by the investigator.
6. Pregnant, lactating or breast-feeding women;
7. Have a urine drug screen detecting illicit drug(s) of abuse (morphine, benzodiazepines, cocaine, amphetamine, THC) or positive alcohol breath test at screening;
8. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab) or human immunodeficiency virus antibody (HIV Ab) at screening;
9. Consumption of, on average, >8 units/day of (methyl)xanthines (e.g., coffee, tea, cola, chocolate) and/or not able to refrain from use during each stay at the CHDR clinic;
10. History or clinical evidence of alcoholism or drug abuse;
11. Smoking of >5 cigarettes/day or equivalent prior to screening and/or not be able to refrain from smoking cigarettes during each stay at the CHDR clinic;
12. Use of prescription, illicit or herbal medication within 7 days or 5 half-lives prior to the first day of dosing, except contraception,and paracetamol. Other current and recent (within 1 month prior to the screening) treatments will be allowed, if judged by the investigator to have no clinical relevance;
13. Participation in a clinical trial with an investigational drug or device within 90 days of first dosing or more than 4 times in the previous year;
14. Loss or donation of blood * 500 mL within 3 months before screening;
15. Subjects of childbearing potential who are unwilling or unable to use a highly effective method of barrier contraception for the duration of the study and for at least 90 days after their last dose of study treatment.
16. All males who are unwilling to practice effective contraception and abstain from sperm donation during the study and who are not willing and able to continue contraception and abstain from sperm donation for at least 90 days after their last dose of study treatment.
17. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
18. Part C, Cohort 7 only: History of spinal cord compression, any other current abnormalities in the lumbar region (skin infection, structural abnormalities in lower spine, etc.), or any other issue that, in the opinion of the investigator, would make CSF collection unsafe
19. Positive SARS-CoV-2 PCR analysis prior to first dosing.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-09-2019
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	YTX-7739
Generic name:	NA

Ethics review

Approved WMO Date:	28-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	16-09-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	22-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2020
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: 21001
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-003169-16-NL
CCMO	NL71070.056.19

Study results

Date completed: 23-07-2020

Results posted: 22-11-2021

First publication
01-01-1900