A Randomized, Double-blind, Placebo-Controlled, 3-Period Crossover Study Followed by 1 Open-label Comparator Period to Evaluate Central Pharmacodynamic Activity of TAK-653 in Healthy Volunteers Using Transcranial Magnetic Stimulation

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The primary objective of the study is to determine whether TAK-653, in comparison to placebo, increases CNS excitability, assessed with TMS-evoked MEP in healthy subjects.Next to that, the study has the following goals: - To determine whether TAK-...

Ethical review	Approved WMO
Status	Completed
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON47989

Source
ToetsingOnline

Brief title
cross-over and open label study to evaluate PD activity of TAK-653

Condition

- Mood disorders and disturbances NEC

Synonym
Depression, depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Depression, Ketamine, Pharmacodynamics, Treatment-resistant Depression

Outcome measures

Primary outcome

The change of peak-to-peak amplitude of the MEP obtained with single-pulse TMS (stimulation intensity: 120% of baseline rMT) at 2* hours after administration of TAK-653 from pre-dosing baseline, compared to placebo.

The change of rMT obtained with single-pulse TMS at 2* hours after administration of TAK-653 from pre dosing baseline, compared to placebo.

Secondary outcome

- Magnitude of long intracortical inhibition (LICI) obtained with paired-pulse TMS (stimulation intensity conditioning pulse and test pulse: 120% of baseline rMT).

- Magnitude of Short intracortical inhibition (SICI) obtained with paired-pulse TMS (stimulation intensity: conditioning pulse 80% of baseline rMT; test pulse: 120% of baseline rMT).

- The resting motor threshold (rMT) obtained with single-pulse TMS assessing ketamine effects, as well as at 24 hours..

- The peak-to-peak amplitude of the MEP obtained with single-pulse TMS (stimulation intensity: 120% of baseline rMT) assessing ketamine effects, as

well as at 24 hours.

Study description

Background summary

TAK-653 is an alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) type glutamate receptor positive allosteric modulator in clinical development as a potential therapeutic for patients with treatment-resistant depression. The TRD field has recently been rejuvenated by the finding that ketamine, an N-methyl-d-aspartate (NMDA) glutamate receptor open channel blocker, has rapid-onset antidepressant properties in the TRD population and in rodent models of depression (eg, reduction of submissive behavior model). The rationale for an AMPA receptor potentiator to treat TRD follows from the observation that the antidepressant actions of ketamine in rodents are blocked with the coadministration of the AMPA receptor blocker NBQX. In addition, ketamine administration causes an increase in extracellular cortical glutamate, which can act on downstream AMPA receptors.A current hypothesis on the mechanisms of the rapid-acting antidepressant effect of ketamine posits that increased AMPA receptor function is a key element in this mechanism. Taken together, these data suggest that by directly potentiating AMPA receptors, TAK-653 may act as a rapid onset antidepressant without the psychotomimetic side effects associated with ketamine administration. TMS is a noninvasive neurostimulation method. Noninvasive brain stimulation techniques like TMS offer an opportunity to study mechanisms of cortical physiology at the systems level of the human brain [2]. The combination of brain stimulation with CNS-active drugs might help assessing the effects of these drugs on brain physiology. Combined with electroencephalography (EEG) and/or electromyography (EMG), both cortical excitability and the modulatory effects of CNS-penetrant drugs can be quantified. Given the absence of evidence for human target engagement or PD activity of TAK-653, the goal
of this study is to leverage a translatable preclinical finding to assess PD activity in healthy subjects. Of specific interest is to determine whether low doses of TAK-653 modulate CNS activity. Based on these data, the study described herein will determine if doses and exposures of TAK-653 correlate with PD effects in TMS-evoked muscle evoked potentials and EEG signals.

Study objective

The primary objective of the study is to determine whether TAK-653, in comparison to placebo, increases CNS excitability, assessed with TMS-evoked MEP in healthy subjects.
Next to that, the study has the following goals:
- To determine whether TAK-653, in comparison to placebo, modulates responses

evoked with paired TMS pulses that capture intracortical circuitry modulation.
- To determine whether ketamine increases CNS excitability assessed with TMS-evoked MEP in healthy subjects.
- To determine the safety and tolerability of TAK-653 when administered as single dose in healthy subjects assessing responses evoked by TMS.

Study design

A randomized, double blind, placebo-controlled, 3-period cross-over study followed by one open label comparator period. The study will include 4 treatment periods, treatment period 1, 2 and 3 are 1 day in duration, period 4 is 2 days in duration, alternating with 3 washout periods of at least 10 days (not to exceed 15 days).

Intervention

Test:
TAK-653 0.5 mg
TAK-653 6 mg
Matching placebo

Open label periode:
Ketamine 0.5 mg/kg

Study burden and risks

This phase 1 trial has been designed to mitigate the known risks associated with AMPA receptor potentiators as a class and the potential risks based on the nonclinical toxicity data and preliminaryclinical data for TAK-653. In addition, this trial has been designed to mitigate the known clinical risks of ketamine. As this trial will be conducted in healthy subjects, there is no expected clinical benefit to trial participants. The principal mitigations for these potential risks include the maintenance of an appropriate safety margin based on nonclinical study use of low doses that yield low drug exposure, appropriate selection of the trial population, the prespecified safety monitoring procedures, and the selection of the trial facility, where close monitoring can be performed and rapid institution of appropriate care can be given. The potential risks associated with AMPA receptor potentiators as a class, the potential risk based on nonclinical toxicity data, and the known clinical risks of ketamine can be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical trial. In addition to the potential risks associated with study drug administration, there is minimal risk associated with trial procedures including scheduled, periodic phlebotomy (limited to <500 mL) and noninvasive procedures including vital sign assessments, electrocardiograms (ECGs), and TMS assessment. Overall, the benefit-risk profile is considered appropriate for

this trial.

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. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be male or female (of nonchildbearing potential) aged 18 to 55 years, inclusive, at the Screening Visit.
4. Have a body mass index >=18.5 and <=30.0 kg/m2 at the Screening Visit.
5. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before the first dose of study drug.

6. Meet the birth control requirements outlined in the protocol.

Exclusion criteria

1. Has a positive alcohol or drug screen.
2. Has a positive pregnancy test.
3. Is a lactating/nursing woman.
4. Has a clinically significant previous or current psychiatric disorder according to the (DSM5) Diagnostic and Statistical Manual of Mental Disorders, including substance use disorder.
5. Has a history of intracranial mass lesion, hydrocephalus and/or head injury or trauma.
6. Has metal objects in brain or skull
7. Has a cochlear implant or deep brain stimulation device.
8. Has a history of epilepsy, seizures, or convulsions.
9. Has a family history of epilepsy, seizures, or convulsions.
10. Has abnormal sleeping patterns (eg, working night shifts)
11. Has a resting motor threshold (rMT) of more than 83% of the maximum stimulator output, measured using TMS-electromyogram (EMG) during screening

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):	21-01-2019
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketamine Rotexmedica
Generic name:	Ketamine
Product type:	Medicine
Brand name:	TAK-653
Generic name:	TAK-653

Ethics review

Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-01-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2019
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	EUCTR2018-004206-26-NL
CCMO	NL68394.056.18

Study results

Date completed: 18-06-2019

Results posted: 19-02-2020

First publication
11-02-2020