A Phase I, Randomized, double-blind, placebo-controlled sequential study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of ADX71441 after single oral ascending doses, and multiple oral ascending dose following a standard dose escalation schedule, randomized, double-blind for placebo and positive control, in normal healthy volunteers

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To evaluate the safety and tolerability of ascending single and multiple oral doses of ADX71441 as compared to placebo in healthy volunteers.To evaluate the pharmacokinetics of orally administered single and multiple doses of ADX71441 and its...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON38582

Source
ToetsingOnline

Brief title
Single and multiple ascending dose of ADX71441 in healthy male volunteers.

Condition

- Neurological disorders NEC

Synonym
increased muscle tone, muscle spasticity

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GABA-B agonist, muscular spasticity, PK-PD

Outcome measures

Primary outcome

Plasma drug concentration of ADX71441 (pharmacokinetics)

Pharmacodynamic evaluation (PD):

- Smooth pursuit,

- Saccadic eye movements,

- Adaptive tracker,

- Body sway,

- VAS (Bowdle, Bond & Lader)

- Learning Maze Task,

- Simple Reaction time task,

- Stop Signal task,

- Visual Verbal Learning Task.

Secondary outcome

Safety parameters:

- Vital signs (BP [standing and lying], HR, RR, Temperature),

- Clinical laboratory: Hematology and Chemistry,

- ECG (holter),

- EEG.

Adverse events during the trial (AEs).

Concomitant medication.

Growth Hormone (GH) plasma concentrations.

Study description

Background summary

ADX71441 is a potent (EC50 40 nM on human receptor) selective positive allosteric modulator (PAM) which activates the GABAB receptor. The principal clinical indication for the potential development of ADX71441 is muscle spasticity. The present study is designed to obtain safety, tolerability and PK data after single and multiple oral administration of increasing doses of ADX71441 in healthy male subjects.

Study objective

To evaluate the safety and tolerability of ascending single and multiple oral doses of ADX71441 as compared to placebo in healthy volunteers.
To evaluate the pharmacokinetics of orally administered single and multiple doses of ADX71441 and its metabolites in healthy volunteers.
To evaluate the pharmacodynamics (including exploratory and clinical safety measures, and Growth Hormone plasma levels) of orally administered single and

multiple doses of ADX71441 in healthy volunteers.

Study design

The study design is a phase I, double blind placebo-controlled with single and multiple doses of AD71441 designed to determine the pharmacokinetics, maximum tolerated dose and pharmacodynamics in humans using a sequential dosing pattern. Up to eighty (80) subjects are planned to be dosed in single ascending dose cohorts and up to sixty-two (62) subjects are planned to be dosed in the multiple ascending dose cohorts.

The study will include 10 single dose (SAD) cohorts between 1 and 100 mg, each of which will include 8 subjects (6 ADX71441 and 2 placebo). The study also plans to include up to four (4) multiple dose cohorts, 3 cohorts with 14 subjects (9 ADX71441, 2 baclofen and 3 placebo once daily for 14 days) and one last cohort (assessment of Growth Hormone levels) with 20 subjects (7 ADX71441 and 13 placebo once daily for 14 days). Subjects will only be enrolled into the MAD cohorts upon completion of treatment and safety review of all preceding single dose cohort subjects.

Subjects in the SAD cohorts will be followed for 14 days and subjects treated in the MAD cohorts will be followed for 27 days after start of dosing.

Medical Monitor (MM), Principal Investigator (PI) and Data Safety Monitoring Board (DSMB) approval is needed for dose escalation prior to treating each cohort of subjects.

Dosage regimens will be in fasting conditions.

Intervention

NA

Study burden and risks

- bruising at the place of venapunction
- medication related: diminish in the muscular power, headache, dizziness, small reduction in body temperature, somnolence.
- medication related (rare): epileptic seizures, allergic reaction, reductions in muscle power and activity.

Contacts

Public

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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. Willing and able to provide written informed consent,
2. Male healthy volunteers 18 to 55 years of age,
3. Subjects with a weight of 75 ±15 kg at screening,
4. In good health as determined by medical history and physical examination,
5. Able to communicate well with the Investigator and research staff and willing and able to comply with all study procedures and visits,
6. Normal arterial blood pressure (BP) and pulse rate or, if abnormal, considered not clinically significant by the Principal Investigator (PI) and MM,
7. Negative test for selected drugs of abuse at the Screening visit,
8. Negative test for alcohol use (breathalyzer) at the Screening visit.

Exclusion criteria

1. Who has a positive hepatitis panel (including hepatitis B surface antigen [HBsAg] and hepatitis C virus antibody [anti-HCV]), or a positive HIV antibody screen,

2. Who previously received ADX71441,
3. Who present with acute or chronic or history of symptoms of gastrointestinal disturbances (GI) or on physical examination have evidence of any clinical signs of acute or chronic GI abnormality (i.e. hemorrhoids, GI bleeding, etc.),
4. Who have a history of chronic uncontrolled medical conditions that may cause a medical emergency in the case of a provoked seizure,
5. Who presents with any clinical abnormality identified during pre-study laboratory tests, full physical examination, vital signs, and ECG, unless deemed acceptable by the PI and the Sponsor,
6. Who present with a diagnosis of epilepsy or history of seizures or fainting spells of unknown or undetermined etiology or has a family history of treatment resistant epilepsy,
7. Who present with or have a history of progressive neurological disorder or focal signs of abnormality on neurological examination,
8. With any history of abnormal EEG or EEG signal suggesting a possible risk of epilepsy, febrile convulsions, etc.,
9. Who present with a history of schizophrenia, bipolar disorder, or other psychotic disorder as defined by DSM-IV_TR,
10. Who have a history of moderate to severe depression, or suicide ideation,
11. Who have a history of allergy, intolerance or photosensitivity to any drug, or who have a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug,
12. Who have a current or recent history (within 6 months of screening) of drug or substance abuse, including alcohol (>= 14 units per week), or who have a significant history of alcoholism or drug/chemical abuse within 6 months prior to the Screening visit (one unit of alcohol equals * pint [285 mL] of beer or lager, one glass [125 mL] of wine, or one shot [25 mL] of spirits),
13. Who drink more than 8 cups daily of beverage containing caffeine,
14. Who currently smoke or have used tobacco products (or equivalent) within 2 weeks prior to the screening visit,
15. Who have undergone surgery or have donated blood within 12 weeks prior to the start of the study,
16. Who currently use any prescription medications/products (with the exception of prescription medications deemed acceptable by the Investigator and Sponsor),
17. Use of any over the counter (OTC), non-prescription preparations (including vitamins, minerals, phytotherapeutic/herbal/plant-derived preparations) within 14 days prior to the Check-in visit, unless deemed acceptable by the Investigator and Sponsor,
18. Who have any clinical condition or prior therapy which, in the opinion of the Investigator, make the subject unsuitable for the study , could compromise subject safety, limit the subject*s ability to complete the study, and/or compromise the objectives of the study,
19. Who have participated to any clinical trial with an investigational drug in the past 3 months preceding study entry,
20. Who have a history of a clinically significant cardiac disease (e.g., myocardial infarction or stroke within 6 months prior to Screening unstable angina, claudication, etc.), or evidence of a clinically significant electrocardiogram (ECG) abnormality at Screening,
21. Who have a history of orthostatic hypotension or evidence orthostatic hypotension at Screening,
22. Who have a history of malignancy, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ,

23. Who have a known Baclofen intolerance (MAD subjects only)

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):	22-04-2013
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lioresal
Generic name:	baclofen
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	ADX71441

Ethics review

Approved WMO

Date:	09-04-2013
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2013
Application type:	First submission
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	EUCTR2013-001238-17-NL
CCMO	NL44272.056.13