A Randomized, Placebo-controlled, Double-blind, Multiple Ascending Dose Study to Investigate Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of JNJ-61393215 in Healthy Subjects.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON45402

Source
ToetsingOnline

Brief title
JNJ-61393215 Phase I MAD study

Condition

- Anxiety disorders and symptoms

Synonym
Anxiety and stress disorders

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag International NV
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: JNJ-61393215, pharmacodynamics, pharmacokinetics

Outcome measures

Primary outcome

1. Safety and tolerability of JNJ-61393215 after multiple consecutive dose

administrations;

2. Pharmacokinetics (PK) of JNJ-61393215 in plasma after multiple consecutive

dose administrations;

3. The effect of JNJ-61393215 on subjective fear and anxiety symptoms elicited

by 35% CO2 double breath inhalation challenge.

Secondary outcome

1. Effect of JNJ-61393215 on physiological response on 35% CO2 double breath

inhalation challenge (i.e. changes in blood pressure and heart rate);

2. Effect of JNJ-61393215 on the startle potentiation in the unpredictable

shock condition during the fear potentiated startle test;

3. Effect of JNJ-61393215 on Alertness/Sedation Through the Bond & Lader Visual

Analogue Scale.

Study description

Background summary

JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential first in class therapy for the treatment of anxiety and stress disorders. The role of OX1Rs in complex emotional behavior is emerging. There is evidence for the overactivation of the OX1R pathway in hyper-arousal states (for example panic attacks), and consequently a selective OX1R antagonist might normalize overexcited networks without inducing sedation.

Study objective

The primary objectives are:
- To investigate the safety and tolerability of JNJ-61393215 after multiple consecutive dose administrations;
- To characterize the pharmacokinetics (PK) of JNJ-61393215 in plasma after multiple consecutive dose administrations;
- To investigate if JNJ-61393215 decreases subjective fear and anxiety symptoms elicited by a 35% CO2 double breath inhalation challenge.

The secondary objectives are:
- To investigate if JNJ-6139325 modulates the physiological responses elicited by 35% CO2 double breath inhalation challenge (i.e, changes in blood pressure and heart rate);
- To investigate if JNJ-61393215 decreases the startle potentiation in the unpredictable shock condition during the fear potentiated startle test;
- To characterize the effect of JNJ-61393215 on alertness/sedation through the Bond & Lader Visual Analogue Scale.

Study design

This study will be a multiple dose phase to establish the anxiolytic pharmacodynamic (PD) properties of JNJ-61393215. For this purpose, a single CO2 inhalation challenge and the fear potentiated startle (FPS) paradigm will be applied as pro-anxiogenic stimuli to investigate whether JNJ-61393215 decreases the subjective fear response and the fear-potentiated startle response, respectively. Two doses of JNJ-61393215 are tested; a high dose in the range of 45 to 90 mg and a low dose in the range of 15 to 30 mg.

Intervention

JNJ-613932, alprazolam or placebo.

Study burden and risks

This study is the first time in humans that multiple doses of JNJ-61393215 will be administered.

This will be the second study with JNJ-61393215 in humans. Nonclinical data and blinded clinical single dose data (study 61393215EDI1001) are available supporting the administration of multiple doses of JNJ-61393215 to humans.

Healthy young male subjects who will receive no therapeutic benefits from study participation will be enrolled in this study. These healthy male subjects will be exposed to an investigational drug, early in clinical development. Women of childbearing potential will not be included, as segment II studies have not been performed yet.

Doses may only be escalated following thorough review of all relevant data collected at lower dose levels. Subjects will be under constant supervision while in the clinic. Subjects will be confined to the clinical until the morning of Day 8, with ambulant visits on Days 9 and 10 for PK sampling.

At high JNJ-61393215 doses changes in coagulation parameters were detected preclinically, as well as an increase in liver weight. Importantly, all observed changes were reversible and can be monitored in the clinic. To address these findings, coagulation and liver parameters will be monitored during all parts of the study to identify potential risks early.

JNJ-61393215 is not genotoxic.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected will not exceed 450 mL, which is considered to be safe and acceptable in comparison to a Red Cross blood donation.

The acute inhalation of CO2 has been developed, validated and technically

innovated over the past years as a reliable challenge model to induce an acute panic reaction that adequately resembles PAs. CO2 and O2 are harmless physiological substances that are inhaled according to a standardized challenge protocol that has been developed by Maastricht University. Numerous studies in several hundred healthy volunteers and patients suffering from panic disorder, social anxiety disorder, post-traumatic stress disorder and major depressive disorder have been conducted according to this protocol over the past 30 years. In the majority of these studies, a mixture of 35% CO2/65% O2 had been administered as either single or double vital capacity inhalation. In all performed studies neither acute nor chronic adverse events have been reported. Also, no serious adverse events have occurred. To guarantee identical safeguards for the current study, the same absolute and relative contra-indications will be maintained and are incorporated into the in- and exclusion criteria of the protocol.

Maastricht Instruments in collaboration with Maastricht University has recently developed the CO2 tolerance tester (CTT). The CTT is a research instrument that safely and reliably induces PA*s by the protocolized administration of inhaled 35% CO2. In addition, the CTT simultaneously measures physiological changes associated with CO2-induced ANS activation such has heart rate and blood pressure. In contrast to previous experimental CO2 set ups, the CTT yields integrated real time information on ANS panic-related parameters following acute CO2 inhalation which can be readily combined with subjective assessments such as fear intensity. The CTT is particularly relevant to research in the field fear-related psychiatric disorders and is a potentially useful tool in CNS drug development with novel anxiolytic compounds.

The Fear Potentiated Startle is a completely safe method in use for over numerous years in research. Volunteers are subjected to loud noises (120 dB for 50 ms). Due to the restricted time frame, no hearing damage is expected. The applied shocks are a nuisance, but not painful.

Contacts

Public
Janssen-Cilag International NV

Turnhoutseweg 30
Beerse 2340
BE
Scientific
Janssen-Cilag International NV

Turnhoutseweg 30
Beerse 2340
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Healthy male subjects between 18 and 55 years of age, inclusive.;2. Subjects must have a body mass index (BMI) between 18.0 and 30.0 kg/m2, inclusive
(BMI = weight/height2).;3. Subject must be healthy on the basis of physical examination, medical history, vital signs, and 12-lead ECG [incl. QTcF <= 450 msec for males and <= 470 msec for females] performed at screening and admission to the clinical unit. Minor abnormalities in ECG, which are not considered to be of clinical significance by the investigator, are acceptable. The presence of Left Bundle Branch Block (LBBB), AV Block (second degree or higher), or a permanent pacemaker or implantable cardioverter defibrillator [ICD] will lead to exclusion.;4. Subjects must be healthy on the basis of clinical laboratory tests performed at screening.
If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.;5. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of contraception e.g., either condom with spermicidal foam/gel/film/cream/suppository during the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug. All men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partner should also use a highly effective method of contraception for at least the same duration. Examples of highly effective contraceptives include implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective

method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.), combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.;6. Subjects must be willing to adhere to the prohibitions and restrictions specified in this protocol.;7. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.;Specific exclusion criteria Part 2:
- Healthy male and female subjects of non-childbearing potential between 18 and 55 years of age, inclusive.;- Before randomization, female subjects must be of non-childbearing potential, defined as:
* Postmenopausal
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
* Permanently sterile
Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.;- Subjects must show sensitivity to a 35% CO2 double breath inhalation challenge at screening or within 12 weeks prior to study drug administration, which is defined as a change in PSL-IV score >=4 with at least 1-point increase for at least 4 of the symptoms specified in the PSL-IV and an increase of at least 25mm on the VAS for anxiety related symptoms.

Exclusion criteria

1. Subject has a history of or current liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, any inflammatory illness or any other illness, though minor deviations, which are not considered to be of clinical significance to both the investigator and to the Janssen Safety Responsible Physician, are acceptable.;2.1 Current or past history of any psychiatric disorder as classified according to DSM-IV or DSM-V.;3.1 Subject has any liver function test (including ALT, AST, gGT, ALP and bilirubin) at screening exceeding 1.5 times the upper limit of normal.;4. Subject has estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2 at screening (provided by the local laboratory).;5. Subject has a heart rate < 50 bpm or > 100 bpm or systolic blood pressure >= 150 mmHg at screening or at admission to the clinical unit.;Specific exclusion criteria Part 2:
- Contraindications to the use of alprazolam per local prescribing information.;- Subject has a personal or family history of sickle cell anaemia.;- Subject has a history of benzodiazepines abuse and/or dependence.;- Subject has a significant cardiovascular history, or suspicion of infarct, cardiomyopathy, cardiac failure, transient ischaemic attack, angina pectoris, cardiac arrhythmias, cerebrovascular accident.;- Subject has a history of significant respiratory

conditions, including asthma, lung fibrosis and non-invalidating Chronic Obstructive Pulmonary Disease.;- Subject has a personal or familial history of cerebral aneurysm.;- Subject has hypertension (i.e. systolic pressure >180 and/or diastolic pressure >100mmHg).;- Subject has epilepsy.

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):	12-01-2017
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alprazolam
Generic name:	Alprazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-12-2016
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-09-2017
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	EUCTR2016-003894-16-NL
ClinicalTrials.gov	NCT03007693
CCMO	NL59843.056.16

Study results

Date completed: 13-10-2017

Results posted: 11-03-2020

First publication
14-10-2018

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File