A first-in-human single-dose escalation study of the safety, pharmacokinetics and pharmacodynamics of the test drug including brain Serotonin Receptor Transporter (SERT) occupancy by Positron Emission Tomography (PET).

Published: 28-12-2009
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Part A: to investigate the safety and tolerability of the drug after a single oral dose in healthy male volunteersPart B: to explore the relationship between dose/exposure of the drug and brain serotonin receptor transporter (SERT) occupancy after a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34991

Source
ToetsingOnline

Brief title
new drug SRD/PET study.

Condition

- Other condition

Synonym
visceral pain

Health condition

pijn aan beschadigde organen

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Visceral pain syndromes

Outcome measures

Primary outcome

Pharmacodynamics: plasma DHPG and NE concentrations, NE/5-HT uptake inhibition,

occupancy of transporter sites

Pharmacokinetics: plasma concentrations, pharmacokinetic parameters

Safety: adverse events, vital signs, ECG-parameters, laboratory parameters,

physical examination

Secondary outcome

n.a.

Study description

Background summary

The drug to be given is a new, investigational compound that may eventually be used for the treatment of pain affecting *soft* organs and body tissue (visceral pain). Visceral pain is the pain we feel when our internal organs are damaged or injured and it is, by far, the most common form of pain.
Few drugs have been approved for specific visceral pain conditions , and current therapies offer limited efficacy.
The drug is a serotonine/norepinephrine (5-HT/NE) dual receptor reuptake inhibitor (SNRI). SNRIs are utilized in the treatment of depression and chronic

pain. SNRIs increase the levels of both serotonin and norepinephrine by inhibiting their reabsorption (reuptake) into the cells in the brain. Serotonin and norepinephrine are both known to play an important part in mood. Elevation of norepinephrine is thought to be necessary to be effective against pain as well.

Study objective

Part A: to investigate the safety and tolerability of the drug after a single oral dose in healthy male volunteers
Part B: to explore the relationship between dose/exposure of the drug and brain serotonin receptor transporter (SERT) occupancy after a single oral dose by direct measurement using 11C-DASB ligand and Positron Emission Tomography (PET)

Study design

Part A

Design:
A randomized, double-blind, placebo controlled, single dose escalating, three period, incomplete cross-over design with two cohorts of eight healthy male subjects each receiving a single oral dose of the drug or placebo (six verum and three placebo); in the first period of the first cohort, two subjects (one on active and one on placebo) will be dosed 24 h before the remaining six subjects of the cohort; treatments for each cohort will be separated by a washout of seven to ten days.

Procedures and assessments
Screening and follow-up:
Clinical laboratory, physical examination, ECG (in triplicate at screening), vital signs; at eligibility screening: medical history, height and weight, urine alcohol and drug screen, HBsAg, anti HCV, anti-HIV 1/2 and genotyping (CYP2D6); to be repeated upon each admission: urine alcohol and drug screen, ECG (in triplicate), vital signs, clinical laboratory and abbreviated physical examination.

Observation period:
3 periods, each period in clinic from -17 h up to 24 h after drug administration on Day 1 followed by ambulatory visits on Days 3 and 5.

Blood sampling:
- for pharmacokinetics of the drug in plasma: pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 96 h post dose, and at follow-up visit
- for pharmacodynamics of DHPG and NE in plasma/posture test: pre-dose and 2, 6 and 24 h post dose

- for pharmacodynamics of DHPG and NE in serum: pre-dose and 2, 6 and 24 h post dose
- for pharmacodynamics of ex vivo NE/5-HT uptake inhibition: pre-dose (evening before dosing) and 2, 6 and 24 h post dose

Safety assessments:
Adverse events: throughout the study; ECG (in triplicate until 24 h post dose): pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 96 h post dose; brief physical examination: once on Day 2; vital signs: once daily on Days -1 to 2 and on Day 3 and 5; clinical laboratory: 24 h post dose.

Bioanalysis:
- analysis of plasma LY2878735 samples using a validated method by PRA International
- analysis of plasma and serum DHPG and NE samples using a validated method by Sponsor
- analysis of ex vivo NE/5-HT samples using a validated method by Sponsor

PART B

Design:
An open label, single dose escalating design with three cohorts of four healthy male subjects each receiving a single oral dose of LY2878735.

Procedures and assessments
Screening and follow-up:
Clinical laboratory, physical examination (brief physical examination at follow-up), vital signs, ECG; at eligibility screening: medical history, urine alcohol and drug screen, height and weight, HBsAg, anti HCV, anti-HIV 1/2, genotyping (CYP2D6), MRI scan; to be repeated upon admission: urine alcohol and drug screen, clinical laboratory and abbreviated physical examination.

Observation period:
One period in clinic from -17 h up to 24 h after drug administration on Day 1 and a baseline visit at approximately 2 weeks prior to dosing for PET scan.

Blood sampling:
- for pharmacokinetics of LY2878735 in plasma: pre-dose and just before Tmax, just after Tmax, 6, 12 and 24 h post dose
- for pharmacodynamics of ex vivo NE/5-HT uptake inhibition: pre-dose and just before Tmax, just after Tmax, 6, 12 and 24 h post dose
PET scan baseline scan, at Tmax and 26 h post dose

Safety assessments:
Adverse events: throughout the study; ECG: pre-dose, at Tmax and 24 h post dose; vital signs and clinical laboratory: pre-dose and 24 h post dose;

abbreviated physical examination: pre-dose and 24 h post dose.

Bioanalysis:
Analysis of plasma LY2878735 samples using a validated method by PRA International.

Intervention

Active substance: LY2878735
Activity: Combined serotonin and noradrenaline transporter inhibitor
Indication: Visceral pain syndromes
Strength: 5 mg, 20 mg and 70 mg
Dosage form: capsules

Treatments
Part A:
Cohort 1:
Period 1: a single oral dose of 5 mg of drug or placebo on Day 1 in the fasted state
Period 2: a single oral dose of 25 mg of drug or placebo on Day 1 in the fasted state
Period 3: a single oral dose of 2.5 mg of drug or placebo on Day 1 in the fasted state
Cohort 2:
Period 1: a single oral dose of 25 mg of drug or placebo on Day 1 in the fasted state
Period 2: a single oral dose of 10 mg of drug or placebo on Day 1 in the fasted state
Period 3: a single oral dose of tbd mg of drug or placebo on Day 1 in the fasted state

Part B:
Cohort 3: a single oral dose of X mg of drug on Day 1 in the fasted state
Cohort 4: a single oral dose of Y mg of drug on Day 1 in the fasted state
Cohort 5: a single oral dose of Z mg of drug on Day 1 in the fasted state

Study burden and risks

Procedures: pain, light bleeding, heamatoma, possibly an infection.

Medication: as LY2878735 will be administered to man for the first time in this study, to date adverse effects in man have not been reported. In previous studies with rats and dogs, in which LY2878735 was administered daily in very high doses convulsions were observed.
The currently available SNRIs have the following most common side effects: loss of apetite, weight, and sleep. There may also be drowsiness, dizziness,

fatigue, headache, sexual dysfunction, and urinary retention. Elevated norepinephrine levels van sometimes cause anxiety, mildly elevated pulse, and elevated blood pressure.

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

Healthy male, age between 18 and 65 years, BMI between 19 and 32.5 kg/m2, non-smoker or moderate smoker, at screening state of health must satisfy the entry requirements. ;Only part B:
Non-exposure to any radiation for diagnostic reasons during work or during participation in a medical trial in the past year, non claustrophobic.

Exclusion criteria

D5a:
Suffering from: hepatitis B, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 90 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

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):	01-02-2010
Enrollment:	38
Type:	Actual

Ethics review

Approved WMO Date:	28-12-2009
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2010

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2010
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	EUCTR2009-017015-14-NL
CCMO	NL31085.056.09