Double-blind, randomized, balanced, placebo controlled, cross-over study of the effect of single oral administration of TM38837 and single oral rimonabant on inhaled tetrahydrocannabinol-induced effects in healthy male volunteers

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Primary objective1. To investigate whether TM38837 attenuates the central effects of THCSecondary objectives2. To explore the effect of TM38837 on THC induced effects on heart rate3. To investigate the effect of 60 mg rimonabant on THC-induced CNS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Appetite and general nutritional disorders
Study type	Observational invasive

Summary

ID

NL-OMON32430

Source
ToetsingOnline

Brief title
Effect of TM38837 and rimonabant on THC-induced effects

Condition

- Appetite and general nutritional disorders

Synonym
obesity

Research involving

Human

Sponsors and support

Primary sponsor: 7TM Pharma
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Cannabinoid systeem, Rimonabant, THC, TM38837

Outcome measures

Primary outcome

Primary study endpoint:

To investigate effect of TM38337 on the central effect of THC using the

following parameters:

• Body Sway

• VAS Bond and Lader (alertness, contentedness, calmness)

• VAS Bowdle (*internal*/*external* perception, *feeling high*)

Secondary outcome

Secondary study endpoints:

To investigate the effect of rimonabant on the central and heart rate effects

(including BDI-II) of THC

To explore the effect of TM38837 on THC induced effect on heart rate

The following pharmacokinetic parameters and dose-normalised pharmacokinetic

parameters will be used for the characterisation of TM38837 as well as for THC:

• Cmax

• Tmax

• T*

• AUC0**

• Subject incidence of AEs and SAEs

• Number and percentage of subjects with clinically significant changes in vital signs (systolic blood pressure, diastolic blood pressure and pulse rate)

• Number and percentage of subjects with clinically significant changes in ECG time intervals (PR, QRS, QT and QTc intervals)

• Number and percentage of subjects with clinically significant changes in laboratory safety tests (haematology, clinical chemistry and urinalysis)

Study description

Background summary

Cannabinoid type 1 (CB1) receptors can be found in the central nervous system (CNS), as well as in peripheral organs, such as the heart, liver, and adipose tissue. CB1-agonist Δ9-tetrahydrocannabinol (THC) has been shown to increase appetite in humans. CB1-receptor antagonists have been shown to decrease appetite and weight in clinical studies. Moreover, CB1-antagonists have been shown to cause beneficial metabolic changes as demonstrated in clinical studies involving patients suffering from metabolic disorders. However, these antagonists caused severe psychiatric side effects. Most likely, these CNS side effects are caused by antagonists binding to and having their effect on CB1-receptors in the brain.

Pre-clinical studies showed beneficial metabolic effects from CB1-antagonists that only work peripherally. Because CB1-antagonists do not show acute effects by themselves, in this study the CB-system of healthy male volunteers will be activated by intrapulmonary administration of CB1-agonist Δ9-THC. We will investigate a peripheral working CB1-antagonist on inhibitory effects of central as well as peripheral THC-induced effects, and its pharmacokinetics (PK).

Study objective

Primary objective
1. To investigate whether TM38837 attenuates the central effects of THC

Secondary objectives
2. To explore the effect of TM38837 on THC induced effects on heart rate
3. To investigate the effect of 60 mg rimonabant on THC-induced CNS and heart rate effects
4. To perform TM38837 PK/PD-analysis, if feasible, to predict the TM38837 concentration that antagonizes THC-induced effects, and to compare the antagonizing potential and the corresponding dose/concentration of TM38837 to 60 mg rimonabant

Study design

Double-blind, double dummy, partially randomized, triple placebo controlled, balanced cross-over, partial parallel study of the effect of single oral administration of TM38837 and single oral rimonabant on inhaled THC-induced effects in 24 healthy male volunteers.

TM38837 or placeboTM38837 will be administered as two single oral doses of 100mg or 500mg. Rimonabant or placeborimonabant will be administered as one single oral dose of 60mg.
THC or placeboTHC will be administered intrapulmonary as five single doses (4 mg) (three on day 1, two on day 2) with 2.5 hour intervals.
All subjects will receive treatment arm 1, 2, 3 and 4. Half of the subjects will receive treatment arm 5a and the other half treatment arm 5b.
All subjects will be dosed with both TM38837 or placeboTM38837, and rimonabant or placeborimonabant, and 5 doses of THC or placeboTHC at every treatment visit.

1 PlaceboTM38837 + Placeborimonabant + 5x PlaceboTHC
2 PlaceboTM38837 + Placeborimonabant + 5x 4 mg THC
3 100mg TM38837 + Placeborimonabant + 5x 4 mg THC
4 500mg TM38837 + Placeborimonabant + 5x 4 mg THC
5a PlaceboTM38837 + 60mg Rimonabant + 5x 4 mg THC
5b PlaceboTM38837 + Placeborimonabant + 5x 4 mg THC

Sequence of treatment arms 1-4 will be completely randomized in a balanced way. Treatment 5 (a or b) will always be the last treatment visit.

Study burden and risks

Expected side effects of THC are: elevated heart rate, feeling high, altered perception of time, lack of concentration, sleepiness, nausea and disturbance of balance.

TM38837 has been tested in humans before. Side effects that were found were

diarrhea and a general feeling of unwell in few subjects and of short duration. No serious adverse events have been reported.

Based on results of previous studies, we do not expect to find side effects caused by rimonabant in this study. In studies with several subsequent dosing days, the following side effects were seen: nausea, infections of the upper airways, stomachache, vomiting, depression, dizziness, diarrhea, itch, transpiration, muscle spasms, fatigue, hot flushes, and attitude changes with depressive symptoms, depressive disorders, anxiety, irritability and nervousness.

The load and the risks involved in participation in this trial are moderate.

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. Subject is able to speak, read and understand the local language of the investigational site, is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent prior to screening evaluations.
2. Legally competent non-african/afro-american/afro-caribebean healthy male with a BMI between 18-28.5 kg/m2, inclusive
3. Age between 18-55 years, inclusive on the day the informed consent is signed.
4. Mild cannabis user for at least one year: cannabis use of no more than once a week, and able to refrain from using cannabinoids from at least 2 weeks prior to the first treatment period to the end of the last study day.

Exclusion criteria

1. History of sensitivity/idiosyncrasy to THC, TM38837 or rimonabant, compounds chemically related to these compounds, or excipients which may be employed in the study or to any other relevant drug used in the past.
2. Any clinically significant cardiovascular (e.g. hypertension), hepatic, renal, respiratory, gastrointestinal, endocrine (e.g. diabetes, dyslipidemia), immunologic, dermatologic (e.g. ancient surgically treated squamous cell carcinomas if considered significant), hematologic (including bleeding disorders), neurologic or psychiatric disease.
3. First degree relative with significant psychiatric disorder

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-03-2010

Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	dronabinol
Product type:	Medicine
Brand name:	Acomplia
Generic name:	rimonabant
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TM38837

Ethics review

Approved WMO Date:	16-12-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-02-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-05-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-017773-38-NL
CCMO	NL30909.058.09