A randomized, double-blind, placebo-controlled study in two parts to investigate in Part 1 the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending dose of RO6799477 in healthy volunteers, and in Part 2 the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple dose of RO6799477 in patients with type 2 diabetes mellitus.

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Main objective Part 1: To assess the safety and tolerability of RO6799477 after multiple ascending oral doses in healthy volunteers.Part 2: To assess the safety and tolerability of RO6799477 after multiple oral doses in patients with type 2 diabetes...

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

Summary

ID

NL-OMON40841

Source
ToetsingOnline

Brief title
Research into the effects of RO6799477 during a longer period

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)
- Schizophrenia and other psychotic disorders

Synonym
Mood disorders, Schizophrenia

Health condition

Mood disorders

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd.

Intervention

Keyword: Mood disorders, Pharmacodynamics, Pharmacokinetics, TAAR 1 agonist

Outcome measures

Primary outcome

PHARMACOKINETIC OUTCOME MEASURES

Parts 1 and 2:

Plasma and urine concentrations of RO6799477 will be measured by a specific and

validated LC-MS/MS method. The following pharmacokinetic parameters will be

estimated using standard non-compartmental methods.

Day 1 and Day 14: Cmax, tmax, AUC0-* and AUCinf (as appropriate), *z, t*, CL/F,

Ae and CLR. Steady state achievement: Ctrough.

Accumulation: RAUC, RCmax, RCtrough.

Pooled plasma samples will also be used for exploratory RO6799477 metabolite

identification.

In Part 1 of the study, blood samples for PK analysis will be drawn before dosing (trough samples as specified in SoA) and immediately (within 30 minutes) before start of the fMRI scan.

Part 1 only:

Population pharmacokinetic (PPK) parameters estimated by non-linear modeling on the CSF concentration-time profiles obtained by applying a sparse sampling strategy.

PHARMACODYNAMIC OUTCOME MEASURES

Glycemic parameters:

o Fasting serum glucose

o Prolactin levels

o Fasting serum insulin (Part 2 only)

• Glycemic blood profiles (Part 2 only):

o 24-h glucose profile (serum)

o 24-h insulin profile (serum).

• Meal tolerance test (MTT):

• Hemoglobin A1c (HbA1c) and fasting serum fructosamine (Part 2 only).

• Scales for appetite sensation:

CNS questionnaire: Self-rating scales at specified timepoints

o Profile of Mood State (POMS):

o ARCI-49 questionnaire (for sedation and dysphoria):

o Columbia Suicide-Severity Rating Scale (C-SSRS) (detection of potential for

suicidality)

• Pupillometry:

• Functional magnetic resonance imaging (fMRI) in Part 1 only.

Secondary outcome

N/A

Study description

Background summary

RO6799477 is a selective partial agonist for TAAR1, which has been extensively profiled in non-clinical procedures predictive of antipsychotic, procognitive, antidepressant and anti-addictive activity with positive results. This leads to the conviction that RO6799477 may constitute an effective drug of a completely new class for the treatment of schizophrenia and mood disorders, targeting symptoms in these diseases which currently are not treatable, such as residual positive symptoms, cognition and negative symptoms, and substance abuse. TAAR1 partial agonists explore a fundamentally new mechanism of action based on the modulation of dopaminergic neurotransmission and, potentially, glutamatergic and serotonergic neurotransmission. In addition, due to its positive effect on glucose metabolism and because it is anticipated that it will not need to be associated with polypharmacology, RO6799477 has the potential to have a more favorable tolerability profile than existing drugs and reduce the incidence of metabolic syndrome in schizophrenia.

Study objective

Main objective
Part 1: To assess the safety and tolerability of RO6799477 after multiple ascending oral doses in healthy volunteers.
Part 2: To assess the safety and tolerability of RO6799477 after multiple oral doses in patients with type 2 diabetes mellitus.

Secondary objectives:
Part 1:
- To investigate the pharmacokinetics of RO6799477 in plasma and in

cerebrospinal fluid;
- To investigate the pharmacodynamic effect of RO6799477 on CNS endpoints and response to a standardized meal;
- To investigate brain penetration of RO6799477 by fMRI.

Part 2:
- To investigate the pharmacodynamic effect of RO6799477 on response to a standardized meal and 24-h glycaemic profiles;
- To investigate the pharmacokinetics of RO6799477 after multiple oral doses in patients with type 2 diabetes mellitus.

Study design

Part 1
Double-blind, randomized, placebo-controlled, sequential,multiple ascending dose study.

Part 2
Double-blind, randomized, placebo-controlled, parallel group, multiple dose study. The start of Part 2 will be contingent on the safety and pharmacodynamic results of Part 1.

Intervention

RO6799477 capsules (using combinations of 10 and 100 mg dosage strengths).
Part 1
In each cohort, subjects will receive daily oral administration of RO6799477 or placebo for 14 days as in-clinic.
Tentative escalation scheme:
The tentative dose escalation scheme will include a minimum of 4 steps.
Cohort 1: 30 mg RO6799477 or matching placebo
Cohort 2: 100 mg RO6799477 or matching placebo
Cohort 3: 300 mg RO6799477 or matching placebo
Cohort 4: 600 mg RO6799477 or matching placebo
The study may be extended to accommodate for additional cohort(s) (e.g. cohort 5 at 900 mg RO6799477 or matching placebo) based on safety, pharmacokinetic and/or pharmacodynamic results, without exceeding 48 subjects in total.

Part 2
Patients will receive daily oral administration of RO6799477 or placebo for 14 days as in-clinic.
• Group A: RO6799477 X mg or matching placebo.
• Group B: RO6799477 Y mg or matching placebo.
with 12 patients in each group (9 active; 3 placebo).
For all the treatment groups, the same number of capsules (mix of matching placebo capsules and capsules of RO6799477 to obtain the chosen dose) will be

taken daily to ensure blinding.
The low dose (X mg) and a high dose (Y mg) of RO6799477 will be selected based on Part 1 data. In any case, the high dose tested in Part 2 will not be higher than the highest safe dose tested in Part 1.

Study burden and risks

Burden for subjects participating in this study:
- Multiple long in-house periods
- Questionnaires: POMS & ARCI49, and physical examinations
- Limited consunption of alcohol, grapefruit juice, food and beverages containing cafeine as wellas use of tobacco
-subjects must refrain from strenuq¡s exercise on the two days preceding admission
- Risk off side effects such as
. Mood changes, such as hyeractivity
. Mild anemia
. Changes in heart rhythm
. Too low blood sugar (hypoglycemia)
- Temporarely prolactin hormone increase.
- Unexpected side effect

Contacts

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Scientific
Hoffmann-La Roche

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part 1: healthy right-handed male subjects 18 to 45 years of age, inclusive.
Part 2: male and female patients with type 2 diabetes, 40 to 65 years of age, inclusive.

Exclusion criteria

(see page 50 of the protocol for the complete list)
Part 1:;Disorders of central nervous system, psychiatric disorders;;Suicidal or homicidal risk, or history of suicide;;Personal or familial history (1st degree) of seizures, epilepsy or other convulsive condition;;Family history (1st degree) of psychosis or mood disorders;;Contraindications for MRI scans;;Contraindications for lumbar puncture; ;History or presence of clinically significant ECG abnormalities;;Angle closure glaucoma, history or current significant ophthalmologic or neurologic condition adversely affecting the pupillometry assessment.;Part 2:;Type 1 diabetes and acquired or secondary forms of diabetes, history of acute metabolic complications (diabetic ketoacidosis or hyperosmolar hyperglycaemia);;Evidence or history of clinically significant diabetic complications such as clinically severe diabetic peripheral neuropathy, nephropathy, pre-proliferative/proliferative diabetic retinopathy;;History of severe symptomatic hypoglycaemia within 6 months prior to screening;;History of weight loss surgery or gastric bypass, gastric stapling, or gastric banding or any other bariatric surgical procedure;;History of eating disorder (e.g., anorexia nervosa and bulimia);;Disorders of central nervous system, psychiatric disorders;;Suicidal or homicidal risk, or history of suicide;;Personal or familial history (1st degree) of seizures, epilepsy or other convulsive condition;;Family history (1st degree) of psychosis or mood disorders;;History or presence of clinically significant ECG abnormalities;;Angle closure glaucoma, history or current significant ophthalmologic or neurologic condition adversely affecting the pupillometry assessment.

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):	19-06-2014
Enrollment:	72
Type:	Actual

Ethics review

Approved WMO Date:	02-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	14-11-2014
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	EUCTR2014-000718-78-NL
CCMO	NL49203.056.14