# OSU6162 as a potential novel drug treatment for Parkinson's disease: effects on dopamine D2 receptor binding in human brain studied using PET.

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To replicate the dose-dependent D2-ligand displacing action of (-)-OSU6162 in the human brain and to determine the optimal dose of (-)-OSU6162 required to achieve a significant amount of D2-ligand displacement in humans.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Movement disorders (incl parkinsonism) |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON36314

**Source**
ToetsingOnline

**Brief title**
Effects of OSU6162 on dopamine D2 receptor binding in human brain.

### Condition

- Movement disorders (incl parkinsonism)

**Synonym**
Parkinsons disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum

**Source(s) of monetary or material Support:** Hersenstichting

## Intervention

**Keyword:** dopamine, dyskinesia, OSU6162, Parkinson

## Outcome measures

### Primary outcome

Striatal binding potential (BPND) values will be used as outcome measure.

Striatal D2 receptor occupancy (%) will be calculated according to: occupancy =

100 * (1 * BPOSU/BPbaseline).

### Secondary outcome

nvt

# Study description

### Background summary

Rationale: Chronic levodopa therapy in Parkinson*s disease (PD) is associated with the development of disabling dyskinesias (involuntary movements with a choreic or dystonic character). After five years of levodopa treatment approximately 30% of patients will suffer from dyskinesias, increasing to 60% after 10 years of treatment (1). The development of anti-dyskinetic agents is therefore an important challenge. An interesting class of drugs are the so-called dopamine stabilizers, which cause dopaminergic inhibition in a state of elevated dopamine function, and enhance dopaminergic signalling under conditions of low dopaminergic tone (2). Conceivably, such drugs might reduce dyskinesias in PD by inhibiting dopaminergic signalling while at the same time avoiding increasing parkinsonism associated with low dopamine levels. (-)-OSU6162 is one of these compounds. Preliminary case studies in advanced PD patients using single dose intravenous infusion of (-)-OSU6162 have shown a reduction in levodopa-induced dyskinesias up to 3* hours after infusion. Studies in animal models of PD, including the MPTP-treated monkey, have shown that (-)-OSU6162 antagonizes both the expression and the development of levodopa-induced dyskinesias. The mechanism of action of (-)-OSU6162 remains to be fully elucidated. Preclinical studies are indicative of positive allosteric modulatory effects on dopamine D2L receptors, and orthosteric antagonistic effects on D2L and D2S receptors. In the monkey, administration of (-)-OSU6162

reduced striatal binding of the selective D2-antagonist [11C]raclopride by an unexpectedly high level of 76% (3), which might indicate that the binding of dopamine to its receptor can indeed be made tighter with (-)-OSU6162. The D2-ligand displacing potential of (-)-OSU6162, as an indication for a positive allosteric modulatory effect of (-)-OSU6162, has never been studied in the human brain.

**Study objective**

To replicate the dose-dependent D2-ligand displacing action of (-)-OSU6162 in the human brain and to determine the optimal dose of (-)-OSU6162 required to achieve a significant amount of D2-ligand displacement in humans.

**Study design**

[11C]raclopride PET scanning will be performed twice on the same day in twelve male healthy volunteers, aged 50-60 years, before and after the administration of a single oral dose of (-)-OSU6162. Initially, the effect of 30 mg of (-)-OSU6162 will be determined in two individuals. After this first dosing of 30 mg, the data will be analyzed and the effect and possible side effects will be discussed in the team to decide on the next dosage. The dosing schedule is adaptable according to findings with the previous dose, including a reduction in dose. Steps in dose escalation will be of 15 mg up to a dose of 60 mg with a final increase in dose of 30 mg up to a dose of 90 mg in a single step. For the dose with optimal displacement of [11C]raclopride, the group will be expanded to six individuals. The time interval between the two [11C] raclopride PET scans will be four hours. The second scan will be performed one hour after the single oral dose of (-)-OSU6162.

**Study burden and risks**

Venous sampling
There is a very small risk of infection and bleeding associated with intravenous catheters, which is prevented by proper techniques.

Radiation exposure
The effective dose equivalent (EDE) of 1 PET study with [11C]raclopride is 2,5 mSv. For comparison, the natural background radiation dose in the Netherlands gives an annual dose of 2 - 2.5 mSv. Thus, the total radiation exposure of one PET study with [11C]raclopride is within an acceptable range. In case of previous exposure to radioactivity, subjects will be eligible if the yearly cumulative dose due to exposure to radiation remains below 10 mSv.

Administration of (-)-OSU 6162
Preclinical safety and toxicology studies have been performed by Pfizer (formerly Upjohn/Pharmacia); IND was submitted to FDA by Pharmacia. Swedish

drug administration authorities (Läkemedelsverket) allowed clinical studies up to 28 days duration. Safety data for (-)-OSU6162 are available from a British phase I study using single oral doses up to 200 mg (7). Potential adverse effects of (-)-OSU6162 administration are on the central nervous system and the cardiovascular system. Single oral doses of (-)-OSU6162 up to 150 mg are well tolerated; side effects are mild to moderate and involve dizziness, headache, nausea, paresthesias, taste perversion, and somnolence. Safety monitoring will include ECG, heart rate, blood pressure and QTc interval measurements. The maximum dosage of (-)-OSU 6162 in the proposed study will be 90 mg oral.

## 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

Investigational group:

healthy volunteers (males)
Age between 50-60 years
Good physical health evaluated by medical history, physical (including neurological) examination RDC (Research Diagnostic Criteria) diagnosis never mentally ill

### Exclusion criteria

Exclusion criteria include a history of a neurological or psychiatric disorder, the use of any centrally active medication, drug abuse (a toxicology screening of urine will be performed to detect opiates, cocaine, amphetamines, cannabis, methadone, benzodiazepines and barbiturates), and participation in other studies involving radiation exposure.

## Study design

### Design

**Study type:** Observational invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 22-07-2011 |
| Enrollment: | 12 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 29-03-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 03-05-2011 |

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| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

# 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 | EUCTR2010-022419-21-NL |
| CCMO | NL33613.029.10 |