# A Combined Escalating Single Oral Dose and Multiple Oral Dose Trial investigating Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of SCH 900479 in Healthy Postmenopausal Female Subjects

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Primary:To investigate the safety and tolerability of single oral administration of study medication in healthy postmenopausal females (Part I)To investigate the general safety and tolerability of the study medication in healthy postmenopausal...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Menopause related conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON34172

**Source**
ToetsingOnline

**Brief title**
SCH 900479 FIM study

### Condition

- Menopause related conditions

**Synonym**
hot flashes, Menopausal symptoms

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Schering-Plough
**Source(s) of monetary or material Support:** Farmaceutische Industrie

## Intervention

**Keyword:** Hot flash, Menopausal symptoms, SCH 900479

## Outcome measures

### Primary outcome

- Pharmacodynamics

- Pharmacokinetics

- Safety

### 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 menopausal symptoms. Hot flashes are the most common symptom related to menopause. A hot flash, or flush, is the spontaneous sensation of warmth, often associated with perspiration, palpitations, and anxiety, resulting from a dilatation of the blood vessel diameter to release the warmth as quick as possible.
Oestrogen (a hormone involved in the regulation of the menstrual cycle and pregnancy) has been used as a hormone supplement for nearly 60 years to treat postmenopausal symptoms. However, it has the potential to induce growth of the endometrium ((inner cell layer of the uterus) which may lead to malignant tumors of the endometrium. This risk can be reduced by concurrent administration of progestogen (a hormone involved in the regulation of the menstrual cycle and pregnancy). In combination with oestrogen treatment, progestogen treatment commonly causes regular and/or irregular vaginal bleeding, which is unacceptable for many postmenopausal women. A major drawback

of this combined therapy is that it may lead to an increased risk of breast cancer.
It is expected that the compound will be effective for the treatment of menopausal symptoms, whilst not inducing the growth of the endometrium and thereby not increasing the risk of malignant tumors of the endometrium.

## Study objective

Primary:
To investigate the safety and tolerability of single oral administration of study medication in healthy postmenopausal females (Part I)
To investigate the general safety and tolerability of the study medication in healthy postmenopausal females following once daily oral administration of escalating doses for 10 days (Part II)

Secondary:
To investigate the single dose pharmacokinetics (PK) of the study medication and its active metabolite following single oral administration (Part I)
To investigate the steady state PK of the study medication and its active metabolite following once daily oral administration for 10 days (Part II)
To investigate the LH effects of the study medication following single oral administration (Part I)
To investigate the LH effects of the study medication following once daily oral administration for 10 days (Part II)

Exploratory :
To explore effects of the study medication on FSH following single oral dose administration, and following once daily oral administration for 10 days
To explore effects of the study medication on SHBG following daily oral administration for 10 days
To explore and, if possible, identify the major metabolites of the study medication in plasma and urine
To explore if Provera® induces a withdrawal bleeding after completion of the study medication treatment for 10 days as biomarker for uterine safety

Optional:
To explore the effects of the study medication on NTx following daily oral administration for 10 days
To compare the pharmacodynamic effects (LH, FSH, SHBG and Provera® challenge ) of a full ER-*/ER-* agonist of 2 mg oral 17*-estradiol (E2) for 10 days and the partial ER-* / ER- * agonist of the study medication for 10 days

## Study design

Design:
Part I:

A randomized, third party blind (within dose level), placebo-controlled, cross-over single rising dose study with two groups of eight healthy postmenopausal females each receiving a single oral dose of the study medication or placebo (six verum and two placebo) in four periods; a washout of at least seven days between dosing

Part II:
A randomized, third-party blind (within dose level), placebo-controlled, multiple rising dose study with four or five groups of eight healthy postmenopausal females each receiving an oral dose of the study medication or placebo (six verum and two placebo) once daily on Days 1-10 and an oral dose of Provera® on Days 15-24 (at home) and one control group of eight healthy postmenopausal females receiving an oral dose of 17-* estradiol once daily on Days 1-10 and an oral dose of Provera® on Days 15-24 (at home)

Procedures and assessments:
Screening and follow-up:
Clinical laboratory, vital signs physical examination, gynaecological examination, 12-lead ECG, pregnancy test; at eligibility screening: medical history, height, weight, elbow breadth measurement, mammography/cervical smear, TVU endometrium (Part II only), drug screen, PT, aPTT, FSH, HBsAg, anti HCV, anti-HIV 1/2; physical exam, drug screen, clinical laboratory, PT and aPTT (Part II only) and pregnancy test to be repeated upon (each) admission

Part I (SAD) :
Observation period:
4 periods, each period in clinic from -17 h up to 48 h after drug administration and ambulatory visits on Days 4 and 5

Blood sampling:
For pharmacokinetics of the study medication and its active metabolite: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 h post-dose
for pharmacodynamics of FSH/LH in serum: pre-dose and 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 h post-dose
for genotyping: pre-dose (Period 1 only)

Safety assessments:
Adverse events: throughout the study; clinical laboratory: once on Day 2; 12-lead ECG pre-dose and 1, 3, 8 and 24 h post-dose; vital signs pre-dose and 1, 3, 8 , 24, 48 and 72 h post-dose

Part II (MAD):
Observation period:
2 periods, first period in clinic from -17 h before drug administration on Day 1 up to 24 h after drug administration on Day 2 and ambulatory visits on Days 3-8, second period in clinic from -17 h up to 48 h after drug administration on

Day 10 (up to 24 h after drug administration for Group 8) and ambulatory visits on Days 12 (Group 8 only), 13 and 14

Blood sampling:
For pharmacokinetics of the study medication and its active metabolite (Groups 3-6 only): pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h post-dose on Day 1, pre-dose on Days 4, 7 and 9 and pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 h post-dose on Day 10 and additionally 3 post-dose samples on Day 7 at around tmax (projected tmax=3 h) will be collected for interim analysis
For pharmacodynamics of FSH/LH in serum: pre-dose and 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 h post-dose on Days 1 and 10 and pre-dose on Days 4, 7 and 9
For pharmacodynamics of SHBG: pre-dose on Days 1, 7, 9, 10 and once at follow-up
For metabolic profiling (Groups 3-6 only): pre-dose and 1, 2, 3, 5, 8, 12 and 24 h post-dose on Days 1 and 10
For genotyping: pre-dose on Day 1

Urine sampling:
For metabolic profiling (Groups 3-6 only): 12 h pre-dose on Day 1 and intervals 0-12 and 12-24 h post-dose on Days 1 and 10
for NTx and creatinine: second morning void on Days -1 and 1

Provera® challenge:
Record vaginal bleeding in diary from Day 14 to follow-up

Safety assessments:
Adverse events: throughout the study; physical examination: once on Days -1, 5 and 11; PT and aPTT: once on Day 10; clinical laboratory: pre-dose on Days 1, 4 and 7 and 24 h post-dose on Day 10; 12-lead ECG: pre-dose and 1, 3, 8 and 24 h post-dose on Days 1 and 10 and pre-dose and 3 h post-dose on Days 4 and 7; vital signs (supine and standing; including oral temperature): pre-dose and 1, 3, 8 and 24 h post-dose on Days 1 and 10, pre-dose and 3 h post-dose on Days 4 and 7 and once on Day 12

Bioanalysis:
Analysis of plasma the study medication and its active metabolite using a validated method by Sponsor
analysis of serum FSH/LH samples using a validated method by Sponsor
analysis of SHBG samples using a validated method by Sponsor
metabolic profiling in plasma and urine by Sponsor
analysis of urine NTx and creatinine samples using a validated method by Sponsor
genotyping by Sponsor

**Intervention**

Active substance: SCH 900479,17-* estradiol, Provera®

**Study burden and risks**

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

# Contacts

**Public**
Schering-Plough

2015 Galloping Hill Road
NJ 07033, Kenilworth
US
**Scientific**
Schering-Plough

2015 Galloping Hill Road
NJ 07033, Kenilworth
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

- Age 45-65 years old
- BMI: 18-32
- Post-menopausal for at least one year or at least 6 months without menstrual cycle and FH levels higher than 40mLU/mL
- Non-smoking or did not smoke in the last 3 months prior screening

## Exclusion criteria

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 60 days from the start of the study or in case of donating more than 1 liter of blood in the 10 months prior the start of this study.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 05-10-2010 |
| Enrollment: | 56 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Estrofem |
| Generic name: | Estradiol |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Provera |
| Generic name: | Medroxyprogesteronacetaat |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 17-05-2010 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-08-2010 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-12-2010 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-12-2010 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-04-2011 |
| 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 | EUCTR2010-020740-35-NL |
| CCMO | NL33435.056.10 |