A SINGLE AND MULTIPLE ASCENDING DOSE TRIAL INVESTIGATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ORALLY ADMINISTERED SP-35454 IN HEALTHY POSTMENOPAUSAL WOMEN

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The objectives of the trial are:1. To investigate the tolerability and safety of SP-35454 following single and multiple dose oral administration.2. To investigate the single and multiple dose pharmacokinetics of SP-35454 and its metabolite SP-...

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

Summary

ID

NL-OMON42209

Source
ToetsingOnline

Brief title
SAD and MAD of SP-35454 in healthy postmenopausal women

Condition

- Other condition

Synonym
osteoporosis

Health condition

postmenopausal osteoporosis

Research involving
Human

Sponsors and support

Primary sponsor: Shin Poong Pharm. Co. Ltd
Source(s) of monetary or material Support: Shin Poong Pharm. Co. Ltd;#1203 15cha Daeryng Techno Town Gwanyang-dong 224-5;Dongang-gu;Anyang-si Gyeonggi-do Korea

Intervention

Keyword: PD, PK, Safety, Tolerability

Outcome measures

Primary outcome

Safety, PK and PD

Secondary outcome

none

Study description

Background summary

SP-35454 is currently in development for the treatment of postmenopausal osteoporosis. Primary or involutional osteoporosis develops as a result of excessive age-related bone loss. Age and menopause are the two main determinants of osteoporosis. The cessation of ovarian production of oestrogen, at the time of the menopause, results in an accelerated rate of bone loss in women. Most of the therapeutic agents currently available for the treatment of osteoporosis are unable to induce bone formation, and have limited utility in the management of severe osteoporosis. The ideal treatment, especially from the viewpoint of reducing fractures, would be capable of both inhibiting bone resorption and also accelerating bone
formation. Pharmacology data indicate that SP-35454 has a dual action: inhibition of bone resorption and stimulation of bone formation by modulating the *Transcriptional co-activator with PDZbinding motif* (i.e. TAZ). The safety and tolerability of SP-35454 were assessed through a series of non-clinical toxicity (incl. genotoxicity) and safety pharmacology studies, which indicated

that SP-35454 is generally very well tolerated, and that undue side effects are not likely to occur. Only relatively minor effects were observed (a slight decrease in group mean body weight gain in
the 4 weeks rat study, minimal mononuclear cell infiltration in the skeletal muscle of male rats dosed at 1000 mg/kg/day for 4 weeks, vomiting at all dose levels as well as abnormal content [purple staining] of feces at 1000 mg/kg/day in the 4 weeks dog study, decreased red blood cell count after 4 weeks of treatment [dog], and at the end of the recovery period at 1000 mg/kg/day and sedation and abnormal gait in the rat central nervous system [CNS] safety pharmacology study at some time points at 300 and 1000 mg/kg). None of these effects were considered adverse.
Inhibition of the human ether-à-go-go-related gene (hERG) tail current was observed at 0.30 (17%) and 1.18 µM (45.9%) (i.e. 1.18 µM equals 0.63 µl/mL), however no effects on cardiovascular parameters were observed after dosing of SP-35454 up to a dose level of 1000 mg/kg to dogs (both after single dosing and after a 4 weeks dosing period). In addition, based on the calculated hERG index (i.e. 131), the risk on clinically relevant effects on hERG channels is considered low. Toxicokinetic parameters in both rats and dogs (to a lesser extent than in rats) were found to
increase less than proportionally with the administered dose (between 100 and 1000 mg/kg). In the rat there was a trend towards somewhat higher exposure in females compared to males (at Day 28). In the dog this sex difference was more pronounced and up to 5-fold higher maximum plasma concentration (Cmax) and up to 7-fold higher area under the plasma concentration-time curve (AUC) values were observed in the female dog, as compared to the male dog. In both species an extreme variability in plasma concentrations was observed. Based on the data package presented in the Investigator*s Brochure of SP-35454, it is concluded that SP-35454, with its dual pharmacological activity on bone resorption and bone
formation, may be an effective compound for the treatment of osteoporosis, with a very favorable safety profile. This compound profile supports further clinical and non-clinical development of SP-35454.

Study objective

The objectives of the trial are:
1. To investigate the tolerability and safety of SP-35454 following single and multiple dose oral administration.
2. To investigate the single and multiple dose pharmacokinetics of SP-35454 and its metabolite SP-35454M8 following single and multiple dose oral administration.
3. To investigate the effect of SP-35454 on biochemical markers of bone turnover following multiple dose administration of SP-35454.
4. To explore and identify metabolites of SP-35454 in plasma and urine.
5. To collect blood samples from postmenopausal women treated with SP-35454 to bank deoxyribonucleic acid (DNA) for future association studies of genotype with the pharmacokinetic (PK), pharmacodynamic (PD) and safety characteristics

obtained in this trial.
6. To investigate the effect of food on the pharmacokinetics of SP-35454 following single dose oral administration.

Study design

Trial design This first-in-human (FIH) trial will be a double-blind, randomized, placebo-controlled, single-center trial. For the single dose part a partial alternating cross over design and for the multiple dose part a parallel group design will be applied. Eligible subjects should fulfill all the inclusion criteria and none of the exclusion criteria.

In the single dose part the effects of 6 (tentative) single orally administered ascending doses of SP-35454 or placebo will be investigated alternately dosed to two groups of 8 healthy postmenopausal women. For each dose 6 subjects will receive active treatment and 2 subjects will receive placebo
.
The tentative dosing schedule is as follows: the first single dose will be an oral dose of 5 mg, followed by the tentative single doses 25, 100, 300, 600 and 1200 mg, administered under fasted conditions.

Dose escalation to the next dose level will be done after evaluation of the safety and the first 24-hour PK results of the previous dose.
The single dose part will be completed by a food effect investigation; the fifth dose (tentative) will be given following the intake of a high calorie/high fat breakfast (800-1000 kcal, ± 50% fat from the total calorie content) to the same subjects as who received this dose in fasting conditions. Thus, in total, SP-35454 will be administered as a single dose at seven occasions.

The first single dose period will have a staggered start spread over 3 days: the first sub-group (2 subjects) will receive trial medication (one on active treatment, one on placebo) at least 24 hours prior to the second sub-group (3 subjects), and the second sub-group will receive trial medication at least 24 hours prior to the third sub-group (3 subjects). The second placebo subject will be randomized to either second or third sub-group.

In the multiple dose part 4 (tentative) multiple ascending doses of SP-35454 will be administered for 28 days to 4 parallel groups of 8 postmenopausal women each. For each dose 6 subjects will receive active treatment and 2 subjects will receive placebo. First dosing in the multiple dose part will in principle commence after completion of the fifth dose (D5; fasting) dose level of the single dose part. The next multiple dose group starts after evaluation of the 2-weeks safety results of the previous multiple dose group. In the multiple dose part, SP-35454 will be taken under fasted conditions.

Intervention

SAD: The study will start with a screening. At the screening a physical examination will take place and a few other standard medical assessments will be performed (ECG,vital signs). Furthermore a blood and urine sample will be taken for laboratory tests and an alcohol breath test and drug screen will be done. During the stay in the clinic the subject will receive the research medication once
on Day 1. Safety will be monitored and will be assessed throughout the study. Venous serial blood samples will be collected. The subjects will be asked for possible side effects on regular basis.
Finally, a follow-up visit will take place.

MAD: The study will start with a screening. At the screening a physical examination will take place and a few other standard medical assessments will be performed (ECG,vital signs). Furthermore a blood and urine sample will be taken for laboratory tests and an alcohol breath test and drug screen will be done. During the stay in the clinic the subject will receive the research medication once
on Day 1 till 28 (both in the clinic and at home). Safety will be monitored and will be assessed throughout the study. Venous serial blood samples will be collected. The subjects will be asked for possible side effects on regular basis.Finally, a follow-up visit will take place.

Study burden and risks

SAD:
SP-35454 is not a registered drug. This drug has not been given to humans before. Animal experiments indicated that SP-35454 is generally very well tolerated, and that there were hardly any side effects. The side effects found were slight decrease in body weight, vomiting, abnormal content (purple staining) of faeces, decreased red blood cell count and some signs of sedation and abnormal gait. These side effects were of a temporarily nature.

The dose levels are selected on the basis of research results in animals. The risk to health at these dose levels is limited but you may experience one of the above mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the trial to minimize these risks.

With any trial product, unusual, unexpected, or previously unreported side effects could occur. Therefore, it is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the trial product.

A blood sample will be drawn approximately 25 times at planned intervals. The total blood volume will be approximately 580 ml over a period of 11 weeks

(group I) or 440 ml over a period of 9 weeks (Group II). The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting or an infection at the blood sampling site can occur.

Your health and possible side-effects from the medication will be closely monitored by the research physicians. If you develop any symptoms during the trial, whether or not you are staying in the clinic at the time, you will be treated by the research physicians. If new information about the safety of the test medication becomes available, you will be informed as soon as possible.

If you notice changes in your physical or mental state, during or after the end of the treatment session, please inform the research physician immediately. This is important for your own safety and for the quality of the research. You will be given an emergency card containing information about the trial and contact details.

MAD
SP-35454 is not a registered drug. This drug has not been given to humans before. Animal experiments indicated that SP-35454 is generally very well tolerated, and that there were hardly any side effects. The side effects found were slight decrease in body weight, vomiting, abnormal content (purple staining) of faeces, decreased red blood cell count and some signs of sedation and abnormal gait. These side effects were of a temporarily nature.

The dose levels are selected on the basis of research results in animals. The risk to health at these dose levels is limited but you may experience one of the above mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the trial to minimize these risks.

With any trial product, unusual, unexpected, or previously unreported side effects could occur. Therefore, it is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the trial product.

The total blood volume will be approximately 270 ml over a period of approximately 8 weeks. The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting or an infection at the blood sampling site can occur.

Your health and possible side-effects from the medication will be closely monitored by the research physicians. If you develop any symptoms during the trial, whether or not you are staying in the clinic at the time, you will be treated by the research physicians. If new information about the safety of the test medication becomes available, you will be informed as soon as possible.

If you notice changes in your physical or mental state, during or after the end of the treatment period, please inform the research physician immediately. This

is important for your own safety and for the quality of the research. You will be given an emergency card containing information about the trial and contact details.

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. Healthy, postmenopausal women.;2. Menopausal status recognized as:;• >=12 months of spontaneous amenorrhea;;• at least 6 months of amenorrhea with serum follicle stimulating hormone (FSH) levels of >= 40 mIU/mL;;• FSH levels of >= 40 mIU/mL following washout of hormone replacement therapy if the menopausal status was not previously confirmed.;3. Age between 45-70 years inclusive at the time of the first dosing administration.;4. Body Mass

Index (BMI) 18.0-30.0 kg/m2 (extremes included) at screening).;5. Good physical and mental health as established by medical history and physical examination and electrocardiogram (ECG) and vital signs recording, results of biochemistry, hematology and urinalysis testing within 21 days prior to the first dose as judged by the Investigator.;6. Subject is a non-smoker for at least 3 months prior to dosing, to be confirmed by a urine cotinine dipstick test.;7. Subject has a negative urine pregnancy test at screening.;8. Washout period from previous treatment for osteoporosis (e.g. oral estrogen and/or progestagen, tibolone or raloxifene or any bisphosphonates) of at least 8 weeks at first dosing.;9. Availability and willingness to complete the study and follow the instructions of the Investigator or trial personnel.;10. Easy venous accessibility.;11. Ability and willingness to sign the ICF prior to screening evaluations.

Exclusion criteria

1. Clinically relevant abnormal laboratory, ECG recordings, vital signs or physical or mental findings at screening as judged by the Investigator. ;2. Clinically significant presence or history of allergy as judged by the Investigator.;3. Positive serology for hepatitis B antigen, hepatitis C antibodies, human immunodeficiency virus (HIV) 1 or HIV-2.;4. History of alcohol or drug abuse within the last 2 years.;5. History of cancer.;6. Surgery of gastro-intestinal tract that might interfere with absorption.;7. Any medication including over the counter products and herbal medications or dietary supplements including products containing Hypericum perforatum (e.g., St. John*s wort) from 14 days prior to Day -1 of the first dosing period, except for occasional paracetamol.;8. Intake of any enzyme affecting drugs from 30 days prior to Day -1 of the first dosing period.4;9. Fluoride therapy for more than 3 months during the previous 2 years.;10. Participation in a trial of an investigational product in the preceding 3 months prior to the first dose or during this trial.;11. Blood donation or blood loss of more than 400 mL in the preceding 3 months before first dosing.;12. Major surgery, fracture, prolonged immobilization (more than 2 weeks) within the 3 months preceding screening.;13. History of hypersensitivity or idiosyncrasy to any of the components of the investigational drug.;14. Positive drug, alcohol or cotinine test at screening and/or admission (Day -1 of the first dosing period). Urine will be tested for the presence of benzodiazepines, opiates, amphetamines, cocaine, cannabinoids, and barbiturates.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2015
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SP-35454
Generic name:	Nap

Ethics review

Approved WMO Date:	19-02-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-09-2015
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	EUCTR2014-004191-33-NL
CCMO	NL52380.056.15
Other	Not yet assigned