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A first in human study to investigate the safety, tolerability and pharmacokinetics of single and multiple doses of SMT19969 in male healthy subjects

Submission date
10/04/2014

Recruitment status
No longer recruiting

Registration date
17/04/2014

Overall study status
Completed

Last Edited
06/10/2015

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
SMT19969, the study drug, is a new antibiotic being developed to treat infections of the gut caused by the bacteria Clostridium difficile. If C. difficile multiplies in the gut it can produce toxins (poisons), which cause illness such as diarrhoea and fever. In some cases the infection can be extremely serious and possibly fatal. New medicines need to be developed to effectively treat this infection. SMT19969 has not previously been given to humans and this study has been designed to look at how safe and well-tolerated this study drug is. The study will also measure how much of the drug gets into the blood stream and what affect the drug has on the body. This information will then be used to allow a study of the drug in patients infected with C. difficile.

Who can participate?
A total of 56 fit and healthy male volunteers aged between 18 and 55 years and with a Body Mass Index (BMI) between 18.0 and 32.0 kg/m2 can take part in the study. Volunteers must agree to use 2 acceptable methods of contraception from the time of first dosing until 3 months after the last dose of study drug. Before a volunteer can join the study they will need to be assessed to see if they are suitable and will need to answer questions about all past and present diseases, allergies and all medications, including prescription and over the counter (non-prescription) drugs.

What does the study involve?
The 56 volunteers will be randomly put into different groups to get either a dose of the study drug (SMT19969) or a dummy (placebo). This means that some volunteers will get the active Study Drug (SMT19969) and some will receive placebo. Whether you get study drug or dummy will be determined randomly and volunteers will not know if they receive the study drug or the dummy. In Part 1 of the study, volunteers will be given a single dose of either the study drug or the placebo. In Part 2 of the study, volunteers will be given two doses each day of study drug or placebo for a total of 10 days. Volunteers will need to give samples of blood, urine and faeces during the study so that investigators can measure the amount of study drug in the body and to

take measurements to examine the safety of the study drug. Volunteers will need to stay at the clinical trial unit during their time on the study.

What are the possible benefits and risks of participating?
The risks involved in this study have been carefully assessed and the main objective of the staff at the Clinical Trial Unit is to ensure the safety of volunteers at all times. The overall risks for the study are considered to be minimal although some are unforeseeable as this will be the first time this study drug has been given to humans. This means that there is a chance of a minor side effect and a very remote chance of something serious happening.
The study drug may have side effects which are currently unknown. There is a very small chance that the study drug (as with any drug or pharmaceutical product) may cause an allergic reaction, which in some cases can be severe. This is known as an anaphylactic reaction, which may be characterised by sudden shortness of breath, decreased consciousness and rash, and may require emergency treatment. The study drug when given orally to test animals was found to be almost entirely confined to the gut and there were almost no study drug found in the blood stream. There were no clinically significant side effects identified in animals when the drug was given orally. However it may be possible that the study drug may cause the following for a short period of time after the dosing: change in bowel habits, stomach discomfort, bloating.

Where is the study run from?
The study ran at a Clinical Trial Unit (CRU) in Leeds, UK.

When is the study starting and how long is it expected to run for?
October 2012 to April 2013.

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Dr Ian Foley

Contact information

Type(s)
Scientific

Contact name
Dr Joseph Chiesa

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Additional identifiers

EudraCT/CTIS number

2012-003451-10

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
SMT19969/C001

Study information

Scientific Title
SMT19969 - a phase I, randomised, partially-blind, placebo-controlled study to investigate the safety, tolerability and pharmacokinetics of single and multiple oral escalating doses in male healthy subjects

Study objectives
This is the first time SMT19969 is being administered to man. The principal aim of this study is to obtain safety and tolerability data when SMT19969 is administered orally as single and multiple doses to healthy male subjects. This information together with the systemic and faecal exposure data will help to establish the doses and dosage regimen suitable for administration to patients. A fed/fasted comparison arm is included to investigate the effect of food on the systemic exposure of SMT19969 prior to patient studies.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East of England - Cambridge East; 20/09/2012; ref. 12/EE/0362

Study design
Randomised partially blind placebo-controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Since the study has closed for enrolment we would not be providing the patient information sheet.

Health condition(s) or problem(s) studied

First in man healthy volunteer safety study. Investigational drug is being developed for treatment of C. difficile infections.

Interventions
A partially blind, placebo controlled, randomised study conducted in 2 parts:

Part 1: Comprises of an ascending single oral dose sequential group study (Groups A to D and F) and a food effect evaluation group study (Group E). Groups B to F are double-blinded and Group A is single-blinded. Groups A and B consitst of 4 subjects, 3 receiving single oral doses of SMT19969 and 1 receiving single oral doses of placebo. Groups C to F consist of 8 subjects, 6 receiving single oral doses of SMT19969 and 2 receiving single oral doses of placebo. Subjects receiving SMT19969 in Groups A-F will receive single oral doses of 2, 20, 100, 400, 1000 and 2000mg respectively.

Part 2 is a double-blinded multiple oral dose sequential group study (Groups G and H). Groups G and H consist of 8 subjects, 6 receiving multiple oral doses of SMT19969 and 2 receving multiple oral doses of placebo. Subjects receiving SMT19969 in Groups G and H will receive two daily doses of 200mg or 500mg respectviely for 9 days with a final dose on the morning of day 10.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
SMT19969

Primary outcome measure
To determine the safety and tolerability of ascending single and multiple oral doses of SMT19969 in healthy male subjects.
1. Ongoing daily monitoring for adverse events through questioning by investigator and spontaneous reporting by subjects
2. Assessment of vital signs (supine blood pressure, supine pulse rate and oral body temperature) at 1, 2, 4, 8, 24, 48 and 72 hours post-dose in Part 1 and in Part 2 on Day 1; 2, 4, 8 and 12 hours post-am dose, Days 2, 4, 6 and 8; Pre-am dose and 2 h post am dose and on Day 10; Pre-dose, 2, 4, 8, 12, 24 and 48 hours postdose
3. 12-lead ECG assessment at 2, 6, 24, 48 and 72 hours post-dose in Part 1 and in Part 2 on Day 1; 2 and 8 hours post-am dose, on Days 3 and 7; 2 h post am dose and on Day 10; Pre-dose, 2, 8, 24 and 48 hours post-dose
4. Blood and urine samples will be collected for clinical laboratory evaluations (standard panel of serum biochemistry, urinalysis, haematology and serology) 72 hours post-dose in Part 1 and in Part 2 on Days 1 and 7; Pre-am dose and Day 10; Pre-dose, and 48 hours post-dose
5. Assessment of faecal samples for the presence of Faecal Occult Blood, as voided from 48 to 72 h post-dose in Part 1 and in Part 2 on the first sample voided on Days 4, 9 and 11

Secondary outcome measures
1. To determine the single and multiple oral dose PK of SMT19969 in healthy male subjects.
1.1. SMT19969 will be quantified in blood samples taken in Part 1 at Pre-dose, 1, 2, 4, 8, 12, 24, 48 and 72 hours post-dose and in Part 2 on Day 1; Pre-am dose, 1, 2, 4, 8 and 12 hours post am dose, Days 2 to 9; Pre-am dose and on Day 10: Pre-dose, 1, 2, 4, 8, 12, 24, and 48 hours post-dose

2. To assess the effect of food on the systemic exposure of SMT19969 in healthy male subjects.
2.1. Subjects in Group E will take part in two treatment periods (TP1 and TP2) at least 6 days apart. In TP1 subjects will receive a single 1,000mg oral dose of SMT19969 under fasted conditions and in TP2 will receive a single 1,000mg oral dose of SMT19969 following a high fat meal.
3. To assess the effect of multiple oral doses of SMT19969 on gut flora (via assessment of faecal samples) in healthy male subjects.
3.1. The first faecal sample voided in Part 2 on days -1, 4 and 9 will be pooled and assessed for gut flora composition by quantitative culture of the following bacteria: Bacteroides, Bifidiobacteria, Lactobacilli, total Clostridia, total anaerobes, lactose-fermenting enterobacteriaceae and total aerobes.
4. To determine concentrations of SMT19969 in faecal samples and potentially conduct exploratory work in plasma and faecal samples using Orbitrap analysis (a technique used to look at potential metabolites, degradants and/or biomarkers).
4.1. SMT19969 will be quantified in faecal samples in Part 1 as voided from 0 to 72 h post-dose and in Part 2 on pooled samples voided over a 24 hour period on days 5 and 10.
4.2. Selected faecal and plasma samples may be retained for further analysis of metabolites.

Overall study start date
08/10/2012

Completion date
08/04/2013

Eligibility

Key inclusion criteria
Subjects will be required to satisfy the following criteria at the screening visit unless otherwise stated:
1. Subjects will be healthy males of any ethnic origin between 18 and 55 years of age.
2. Body Mass Index (BMI) between 18.0 and 32.0 kg/m2 inclusive; and a total body weight within the range of 50 kg to 100 kg.
3. Subjects will have given their written informed consent to participate in the study and to abide by the study restrictions

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Male

Target number of participants
56

Key exclusion criteria
Subjects will be excluded from the study if they satisfy the following criteria at the screening visit unless otherwise stated:

1. Male subjects who are not willing, or whose partners are not willing, to use appropriate contraception (such as a condom with spermicidal foam/gel/film/cream/suppository), or are not willing to refrain from donating sperm from the time of the first dose until 3 months after the final dosing occasion.
2. Subjects who have received any prescribed systemic or topical medication within 14 days of the first dose administration unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
3. Subjects who have used any non-prescribed systemic or topical medication (including vitamins and dietary supplements) within 7 days of the first dose administration unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety. Herbal supplements must be discontinued at least 28 days prior to the first dose of trial medication. Exceptions: Paracetamol may be used at doses of <2g/day
4. Subjects who have received any medications, including St John's Wort, known to chronically alter drug absorption or elimination processes within 30 days of the first dose administration unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
5. Subjects who are still participating in a clinical study or who have participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 3 months up to the time of first dose.
6. Subjects who have donated any blood, plasma or platelets in the 3 months prior to screening or who have made donations on more than two occasions within the 12 months preceding the first dose administration.
7. Subjects who have any evidence or history of cardiovascular disease including systemic hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg at screening), resting hypotension (systolic BP <90 mmHg or diastolic BP <50 mmHg at screening) or bradycardia (heart rate <40 bpm at screening).
8. Subjects who consume more than 28 units of alcohol per week within 6 months of screening or who have a significant history of alcoholism or drug/chemical abuse as determined by the Investigator (1 unit of alcohol equals ½ pint [285 mL] of beer or lager, 1 glass [125 mL] of wine, or 1/6 gill [25 mL] of spirits)
9. Subjects with a positive urine drug screen or alcohol breath test result at screening or first admission.
10. Subjects who smoke in excess of 15 cigarettes/day.
11. Subjects with, or with a history of, any clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic or allergic disease (including significant drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing) as determined by the Investigator.
12. Subjects who have had a clinically significant illness within 4 weeks of the start of dose administration as determined by the Investigator.

Date of first enrolment
08/10/2012

Date of final enrolment

08/04/2013

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Covance Clinical Research Unit (CRU) Ltd.
Leeds
United Kingdom
LS2 9LH

Sponsor information

Organisation
Summit Corporation PLC (UK)

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Sponsor type
Industry

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ROR
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Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	25/02/2015		Yes	No
HRA research summary			28/06/2023	No	No