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Study of tadalafil 20 mg oral film and soft-gel capsules versus Cialis® (tadalafil) 20 mg tablet in healthy male volunteers

Submission date 20/02/2018	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 19/11/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 19/11/2018	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
The main aim of this study is to measure the movement of the drug tadalafil within the body when it is taken either as an oral film without water, as a soft-gel capsule and as a tablet, as a single dose in 15 healthy male volunteers in fasting conditions. The secondary aim is to assess the safety and tolerability (side effects) of each treatment.

Who can participate?
Healthy male volunteers aged 18 to 50

What does the study involve?
Each participant receives the three treatments in three different study periods in a random order, separated by breaks of 14 days. In each study period, 22 blood samples are collected from each participant, starting from right before taking the drug and up to 72 hours thereafter.

What are the possible benefits and risks of participating?
There is no direct benefit of participation in the study.

Where is the study run from?
Algorithme Pharma (Canada)

When is the study starting and how long is it expected to run for?
March 2017 to December 2017

Who is funding the study?
IBSA Institut Biochimique SA

Who is the main contact?
Mr Stefano Rovati

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
17CDN-TAD03

Study information

Scientific Title
Single dose crossover comparative bioavailability study of tadalafil 20 mg oral film and soft-gel capsule versus Cialis® (tadalafil) 20 mg tablet in healthy male volunteers

Study objectives
Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE) type 5. Tadalafil is indicated for the treatment of erectile dysfunction. Tadalafil is also indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia and in men having both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia.

The recommended dose of tadalafil for on-demand use for erectile dysfunction is 10 mg taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients. The recommended dose of tadalafil for once daily use for erectile dysfunction is 2.5 mg per day, taken at approximately the same time every day, without regard to timing of sexual activity. The dosage may be increased to 5 mg based on individual efficacy and tolerability. The recommended dose of tadalafil for once daily use for benign prostatic hyperplasia treatment is 5 mg, taken at approximately the same time each day. The recommended dose of tadalafil for once daily use for the treatment of erectile dysfunction and for benign prostatic hyperplasia is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

After single oral-dose administration, the maximum observed plasma concentration of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined. The rate and extent of absorption of tadalafil are not influenced by food; thus tadalafil may be taken with or without food. Over a dose range of 2.5 to 20 mg, tadalafil exposure increases proportionally with dose in healthy subjects.

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Tadalafil is predominantly metabolized by cytochrome P450 (CYP) 3A4 to a catechol metabolite. The mean oral clearance for tadalafil is 2.5 L/h and the mean terminal half-life is 17.5 hours in healthy subjects.

This single dose study design was selected to adequately characterize the bioavailability of tadalafil in the three formulations in healthy subjects. As this was a bioavailability trial, a control group was not included.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The protocol and the informed consent forms (ICFs) were approved by an institutional review board (IRB), IRB Services on 11/07/2017, and the Amendment 01 of the protocol was approved on 02/08/2017

Study design
Single-dose bioavailability trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Bioavailability study of tadalafil 20 mg oral film and soft-gel capsule versus Cialis® (tadalafil) 20 mg tablet

Interventions
Each volunteer received the 3 treatments in 3 different study periods, according to a cross-over design. The randomization scheme was computer-generated.

Test-1: 1 x Tadalafil IBSA 20 mg OF
Test-2: 1 x Tadalafil IBSA 20 mg soft-gel capsule
Reference: 1 x Cialis® (tadalafil) 20 mg tablet

The drug administrations were separated by a wash-out of 14 days. The investigational products were administered on 05/08/2017 for period 1, on 19/08/2017 for period 2, and 02/09/2017 for period 3.

In each study period, 22 blood samples were collected for each subject, starting from right before drug administration and up to 72 hours thereafter. Tadalafil was measured in human plasma using a validated HPLC with MS/MS method (Limit of Quantification = 5.00 ng/mL).

Intervention Type

Drug

Phase
Phase I

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

Primary outcome(s)
Pharmacokinetic profile before and at different timepoints over the 72 h period after single drug administration in each of three study periods: tadalafil blood levels measured using a validated high performance liquid chromatography (HPLC) method with tandem mass spectrometry (MS/MS) detection, the lower limit of quantitation (LOQ) was 5.00 ng/mL

Key secondary outcome(s))
Adverse events reported during the whole clinical phase, together with vital signs, ECGs and standard lab tests before and at the end of the trial

Completion date
12/12/2017

Eligibility

Key inclusion criteria
1. Male, at least 18 years of age but not older than 50 years
2. Non- or ex-smokers
3. Body mass index (BMI) within 18.5 to 30.0 kg/m2, inclusively
4. No clinically significant abnormality found in the 12-lead electrocardiogram (ECG) performed at study entry
5. Healthy according to medical history, complete physical examination (including vital signs and penis examination) and laboratory tests (general biochemistry including lipid profile, hematology and urinalysis)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Male

Key exclusion criteria

Volunteers presenting any of the following will not be included in the study:
1. Presence or history within 28 days of any tongue piercings
2. Presence of partials, braces or dentures
3. Seated pulse rate less than 50 Beats per Minute (bpm) or more than 100 bpm at screening
4. Seated blood pressure below 100/60 mmHg at screening
5. Seated blood pressure higher than 140/90 mmHg at screening and prior to 1st dosing
6. History of significant hypersensitivity to tadalafil or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
7. Presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects
8. History of significant gastrointestinal, liver or kidney disease that may affect drug bioavailability
9. Presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
10. Suicidal tendency, history of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases
11. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 200 msec, QRS <60 msec, QRS >110 msec and QTc > 440 msec) on the screening ECG or other
clinically significant ECG abnormalities
12. Use of organic nitrate medication in the previous 28 days before day 1 of the study
13. Use of PDE 5 inhibitors (such as sildenafil) in the previous 28 days before day 1 of the study
14. Volunteer at increased risk of priapism, including subjects with sickle cell anemia, multiple, myeloma, leukemia, etc
15. Presence or history of non-arteritic anterior ischemic optic neuropathy (NAION)
16. Presence or history of anatomical deformation of the penis (i.e. angulation, cavernosal fibrosis or Peyronie's disease)
17. Known presence of rare hereditary problems of galactose and /or lactose intolerance, lactase deficiency or glucose-galactose malabsorption
18. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
19. Any clinically significant illness in the previous 28 days before day 1 of this study
20. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine,
erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (such as barbiturates,
carbamazepine, glucocorticoids, phenytoin, rifampin and St John's Wort), in the previous 28 days before day 1 of this study
21. Any history of tuberculosis and/or prophylaxis for tuberculosis
22. Positive screening of alcohol and/or drugs of abuse
23. Positive results to HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
24. Volunteers who took tadalafil in the previous 28 days before day 1 of this study
25. Volunteers who took an Investigational Product (in another clinical trial) in the previous 28 days before day 1 of this study
26. Volunteers who have already participated in this clinical study
27. Volunteers who donated 50 mL or more of blood in the previous 28 days before day 1 of this study
28. Donation of 500 mL or more of blood (Canadian Blood Services, Hema-Quebec, clinical studies, etc.) in the previous 56 days before day 1 of this study

Date of first enrolment
04/08/2017

Date of final enrolment
05/09/2017

Locations

Countries of recruitment
Canada

Study participating centre
Algorithme Pharma
1200 Beaumont Ave.
Mount-Royal, Québec
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H3P 3P1

Sponsor information

Organisation
IBSA Institut Biochimique SA

ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Institut Biochimique SA

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available as these PK/safety data refer to a very early stage of clinical development and, based on the outcome of the trial, the two formulations tested were both abandoned and alternate pharmaceutical development programs were initiated in the meantime.

IPD sharing plan summary

Not expected to be made available