Phase I, double-blind, randomized, placebo-controlled trial to examine the safety, tolerability and plasma pharmacokinetics of increasing single oral doses of TMC558445 with and without food, and increasing repeated oral doses in combination with a single dose of TMC310911.

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Single dose:The objectives of Part 1 (single dose escalation part) are to examine the safety, tolerability and pharmacokinetics (i.e., the circulating levels of TMC558445 in your blood over time) of increasing single oral doses of TMC558445, with...

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

Summary

ID

NL-OMON33802

Source
ToetsingOnline

Brief title
Phase I trial to examine TMC558445 and TMC310911.

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Tibotec Pharmaceuticals, EastGate Village, Eastgate, Little Island, CO Cork, Ireland, In Nederland vertegenwoordigd door Janssen-Cilag B.V.
Source(s) of monetary or material Support: TIBOTEC PHARMACEUTICALS;EASTGATE VILLAGE;EASTGATE;LITTLE ISLAND;CO. CORK;IRELAND;IN NEDERLAND VERTEGENWOORDIGD DOOR JANSSEN CILAG B.V

Intervention

Keyword: First in Human., Food-effect., HIV., Pharmacokinetic.

Outcome measures

Primary outcome

Single dose:

The objectives are to examine the safety, tolerability and pharmacokinetics

(i.e., the circulating levels of TMC558445 in your blood over time) of

increasing single oral doses of TMC558445, with and without food.

Multiple dose:

The objectives of Part 2 (multiple dose escalation part) are to examine the

safety, tolerability and pharmacokinetics of increasing repeated oral doses of

TMC558445, followed by a single dose of TMC558445 together with TMC310911 or

DRV to assess whether the combined intake of TMC558445 with TMC310911 or DRV

increases the circulating levels of TMC310911 or DRV in blood.

Secondary outcome

Not applicable.

Study description

Background summary

In this study 2 investigational new drugs and 1 registrated drug are involved.
The 2 new investigational drugs called TMC558445 (from the PEPI family) and TMC310 911 are in process of development for the treatment of Human Immunodeficiency Virus-Type 1 (HIV-1). TMC558445 and TMC310911 are both being developed by Tibotec Pharmaceuticals are not approved for use by the US Food and Drug Administration and other Regulatory Authorities in the European Union (EU). Therefore, they can only be used in a research study.
TMC558445 is a novel molecule with no antiviral activity to be used to enhance the pharmacokinetics profile of a drug. TMC310911 is a novel and potent compound and belongs to a medication class called protease inhibitors (PI). It is assumed to be very active against the HIV-1 virus, the virus that causes AIDS, when other treatments will fail.

TMC114 (darunavir) is a new-generation inhibitor of the Human Immunodeficiency Virus (HIV) protease (an enzyme), marketed under the name of Prezista, and used worldwide to treat patients with HIV-1 infection. TMC114 is approved and commercially available for both treatment experienced (600 mg twice daily) and naïve (800 mg once daily) HIV-infected patients when co administered with low dose of ritonavir (100 mg twice or once daily, respectively) as a pharmacokinetic enhancer. TMC114 is the company's reference standard protease inhibitor and will serve as a comparator for boosting efficacy with TMC558445. More than 3,000 HIV-1 infected subjects have been treated so far with TMC114/rtv in studies in humans. Many of these subjects received TMC114 for at least 1 year. Additionally, approximately 1,300 healthy volunteers have received TMC114 for a period of 1 day up to 2 weeks in studies in humans. The safety of use of TMC114 is well documented and the potential unwanted side effects are summarized below.

Study objective

Single dose:
The objectives of Part 1 (single dose escalation part) are to examine the safety, tolerability and pharmacokinetics (i.e., the circulating levels of TMC558445 in your blood over time) of increasing single oral doses of TMC558445, with and without food.

Multiple dose:
The objectives of Part 2 (multiple dose escalation part) are to examine the safety, tolerability and pharmacokinetics of increasing repeated oral doses of TMC558445, followed by a single dose of TMC558445 together with TMC310911 or DRV to assess whether the combined intake of TMC558445 with TMC310911 or DRV

increases the circulating levels of TMC310911 or DRV in blood.

Study design

The study has a randomized, double blind, placebo-controlled design.

Intervention

Single dose:
Will consist of 6 sessions (Sessions I to VI). Nine subjects will take part in Sessions I, III and V (Panel 1), and 9 other subjects take part in Sessions II, IV and VI (Panel 2). In each session, 6 subjects will take TMC558445 and 3 subjects will take placebo. Over 3 sessions, each subject will receive TMC558445 twice and placebo once.
After completion of Sessions I to VI, 9 subjects (either from Panel 1 or Panel 2, depending on the chosen dose) will have an additional session (Session VII) to investigate a possible effect of food. The dose of TMC558445 will be a dose chosen out of the 6 previously administered doses of Panels 1 or 2. Subjects who received TMC558445 at the selected dose in one of the Sessions I to VI will again receive TMC558445 at the chosen -intermediate- dose, but now in fasted condition. Subjects who received placebo will receive placebo again, also in fasted condition.

Multiple dose:
Part 2 will consist of 4 panels of 9 subjects each. In each panel, 6 subject will receive TMC558445 and 3 subjects will receive placebo. Please find below the treatments per panel.

Group 3 Treatment VIII:
- 100 mg twice daily TMC558445 or placebo for 7 consecutive days.
- 300mg TMC310911 on Day 7

Treatment XI:
- 300 or 600mg TMC310911 on Day 1

Group 4 Treatment IX:
- TMC558445 or placebo twice daily for 7 consecutive days.
(dose to be determined)
- 300mg TMC310911 on day 7

Treatment XI:
- 300 or 600 mg TMC310911 on Day 1 (to be determined).

Group 5 Treatment X:
- TMC558445 or placebo once or twice daily for 7 consecutive days
(dose to be determined)

- 300 or 600 mg TMC310911 on Day 7 (to be determined).

Treatment XI:
300 or 600 mg TMC310911 on Day 1 (to be determined).

Group 6 Treatment XII:
- 200 mg TMC558445 or placebo once daily for 7 consecutive days.
- DRV 800mg on Day 7.

Treatment XIII:
- DRV 800mg on Day 1.

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Study burden and risks

The risks associated with this investigation are linked together with the possible side effects of the investigational products. The burden on the volunteer will continue to work with the recording periods, venapunctions and the introduction of the cannula. All volunteers are closely monitored and supervised by experienced doctors and studystaff for possible side effects. The following tests will be performed during this trial: physical examination, measuring bloodpressure and hart rate, blood- and urine tests, pregnancy test (women only), drugscreen, alcohol tests, ECGs, restrictions in living habits, standardized meals during admission.
Al volunteers will be closely monitored by experienced physicians and staff.

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) 18-60 years;
2) Nonsmoker;
3) BMI 18.0-30.0;
4) Signed ICF
5) Able to comply with protocol requirements
6) Healthy based on the basis of a medical evaluation.

Exclusion criteria

1) History of clinically significant heart arrhythmias;
2) Female except if they are of non-childbearing potential;
3) History or evidence of alcohol and or drug abuse ;
4) Hepatitis A, B en C;
5) Positive urine drug test;
6) Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory or infectious disease;
7) Any history of significant skin disease such as but not limited to rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis or urticaria
8) History of drug allergy;
9) Use of concomitant medication, except for paracetamol and ibuprofen in the 14 before first trial medication intake;
10) Participation in an investigational drug trial within 60 days prior to the first intake of trial medication;
11) Donation of blood plasma within the 60 days preceding the first intake of trial medication;
12) Lab abnormalities.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-02-2009
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Prezista
Generic name:	darunavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TMC310911
Generic name:	TMC310911
Product type:	Medicine
Brand name:	TMC558445
Generic name:	TMC558445

Ethics review

Approved WMO

Date:	26-01-2009

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-02-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2008-008133-10-NL
CCMO	NL26300.040.09