A Single-Dose, Open-Label, Randomized, Replicate Crossover Pivotal Bioequivalence Study in Healthy Subjects to Assess the Bioequivalence of Darunavir 675 mg, Emtricitabine 200 mg, and Tenofovir Alafenamide 10 mg in the Presence of Cobicistat 150 mg when Administered as a Fixed Dose Combination (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide) Compared to the Coadministration of the Separate Agents (Darunavir, Cobicistat, and Emtricitabine/Tenofovir Alafenamide), Under Fed Conditions

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- To evaluate the single-dose PK and pivotal bioequivalence of 3 compounds darunavir (DRV) 675 mg, FTC 200 mg, and tenofovir alafenamide (TAF) 10 mg in the presence of cobicistat (COBI)150 mg when administered as an fixed-dose combination (FDC) (D/C...

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

Summary

ID

NL-OMON49638

Source
ToetsingOnline

Brief title
Bioequivalence Study

Condition

- Immunodeficiency syndromes

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Janssen Sciences Ireland UC
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Bioequivalence, Open-Label, Seperate agents, Symtuza

Outcome measures

Primary outcome

The following PK parameters for Darunavir, Cobicistat, Emtricitabine, and

Tenofovir alafenamide will be determined for each treatment period:

- Cmax maximum observed analyte concentration;

- tmax the actual sampling time to reach the maximum observed analyte

concentration;

- AUClast area under the analyte concentration-time curve (AUC) from time 0 to

the time of

the last measurable (non-below quantification limit [non-BQL]) concentration, calculated by linear-linear trapezoidal summation;

- AUC* AUC from time 0 to infinity, calculated as AUClast + Clast/*z, where Clast is the last observed measurable (non-BQL) concentration; extrapolations of more than 20.00% of the total AUC are reported as approximations;

- Clast last observed measurable (non-below quantification limit [BQL]) analyte concentration;

- tlast the actual sampling time of the last measurable (non-BQL) analyte concentration

- *z apparent terminal elimination rate constant, determined by linear regression using the terminal log-linear phase of the log-transformed concentration vs. time curve;

- t1/2 apparent terminal elimination half-life, defined as 0.693/*z.

Secondary outcome

The study will include the following evaluations of safety and tolerability:

• Adverse events

• Clinical laboratory

• Vital signs

• ECG

• Physical examination

Study description

Background summary

During this study the participant will receive 4 different study compounds that can be used for the treatment of infection with Human Immunodeficiency Virus type 1 (HIV-1). HIV targets immune cells (T-cells) and kills them. This type of immune cell is important for coordinating the immune response to infections. Therefore, the body is more susceptible to new infections when there are not enough T-cells. The reduced effectiveness of the immune system may over time develop in AIDS. It is estimated that in 2018 approximately 38 million people worldwide were living with HIV and that it resulted in about 770 000 HIV-related deaths. Treating HIV requires a combination of drugs, which makes it harder for patients to follow directions. Therefore a combination tablet that contains multiple drugs is under investigation.

A short description of each compound is given below:
- Darunavir is a drug that is used for the treatment of HIV. It works by blocking the activity of a HIV-related protein (HIV-1 protease) that is important to generate new viruses. This prevents other cells from being infected by the virus.
- Cobicistat is a medication that reduces the activity of a group of liver proteins (CYP3A) that are important for breaking down chemicals (such as drugs) in the body. Cobicistat can thereby prolong the activity of other administered drugs.
- Emtricitabine is a drug that inhibits the growth of the virus that causes HIV. It works by slowing down the copying of virus DNA and thereby prevents the virus from multiplying.
- Tenofovir alafenamide is a medication that will be broken down in the body to its active form: tenofovir. Tenofovir works in a similar way as emtricitabine and slows down the multiplication of the virus on DNA level.

Study objective

- To evaluate the single-dose PK and pivotal bioequivalence of 3 compounds darunavir (DRV) 675 mg, FTC 200 mg, and tenofovir alafenamide (TAF) 10 mg in the presence of cobicistat (COBI)150 mg when administered as an fixed-dose combination (FDC) (D/C/F/TAF) compared to the co-administration as the separate commercial formulations (DRV 1×600 mg and 1×75 mg tablet and F/TAF 1×200 mg/10 mg tablet and COBI 1×150 mg tablet), under fed conditions, in healthy subjects.
-To evaluate the single-dose PK and relative bioavailability of COBI 150 mg in the presence of DRV 675 mg, FTC 200 mg, and TAF 10 mg when administered as an FDC (D/C/F/TAF) compared to co-administration as the separate commercial formulations (COBI 1×150 mg tablet in the presence of DRV 1×600 mg and 1×75 mg tablet and F/TAF 1×200 mg/10 mg tablet), under fed conditions, in healthy subjects.
-To evaluate the short-term safety and tolerability of co-administration of DRV 675 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg, under fed conditions, in healthy subjects.

Study design

The study will consist of 4 periods during each the participants will stay in the research center for 5 days (4 nights).
Day 1 is the first day of administration of the study compounds. The participants are expected at the research center at 10:00 AM in the morning prior to each day of administration of the study compounds, so on Day -1 of each period. In each period, the participant will leave the research center after staying 4 nights (so on Day 4). There will be at least 7 days between treatments in each period. The participant will be asked to return to the research center approximately 7 - 10 days after the last administration of the study compound (Period 4) to check their health for the last time.

Intervention

During the course of this study the participant will receive 2 treatments twice, for a total of 4 treatments. They will receive the following doses of the study compounds: 675 mg Darunavir, 200 mg Emtricitabine, 10 mg Tenofovir alafenamide and 150 mg Cobicistat, composed as follows:

Treatment A:
• 1 single tablet combining 675 mg darunavir, 200 mg emtricitabine, 10 mg tenofovir alafenamide and 150 mg cobicistat

Treatment B:
• 1 tablet containing 600 mg darunavir
• 1 tablet containing 75 mg darunavir
• 1 tablet combining 200 mg emtricitabine and 10 mg tenofovir alafenamide
• 1 tablet containing 150 mg cobicistat

The order of treatments is determined by randomization (ABBA or BAAB).
The study compounds will be given in the morning as oral tablets with 240 milliliters (mL) of (tap) water.

Study burden and risks

Four clinical studies have been completed with the Darunavir (D) /Cobicistat (C) /Emtricitabine (F) /Tenofovir alafenamide (TAF) fixed dose combination (FDC) tablet in 199 healthy volunteers. The most frequently observed side effects (seen in more than 10 percent of research participants) of D/C/F/TAF were diarrhea, headache, and skin rash, mostly mild or moderate in severity. Skin rash, when it occurs, may be accompanied with fever and/or an increase in liver enzymes. It usually develops within the first 4 weeks of treatment with D, is often mild or moderate in severity, often resolves within one week and does not necessarily lead to treatment interruption. In some cases, the rash has been severe or life-threatening. Rare cases of Stevens-Johnson syndrome and

very rare cases of other severe skin reactions have been reported in patients taking D in combination with other anti-HIV drugs, as well as other medications. The signs and symptoms of severe rash may include mouth and lips sores or ulcers, fever, itching, weakness, fatigue, malaise, muscle or joint pain, skin conditions (blisters, hives, boils and peels), swollen eyelids or red or inflamed eyes (conjunctivitis), trouble swallowing or breathing, inflammation of the liver (hepatitis) and/or increase of white cells in the blood (eosinophilia).

Drawing blood and/or insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising.
In total, no more than than 500 milliliters (mL) of blood from will be taken from the subjects over the entire course of the study.

To make a heart tracing (ECG), electrodes (small, plastic patches) will be pasted at specific locations on your arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

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

Subjects must satisfy the following criteria to be enrolled in the study:

1. Must be a man or woman between 18 and 55 years of age, extremes included, at screening.
2. Must have a body mass index (BMI; weight [kg]/height2 [m]2) between 18.5 and 30.0 kg/m2 (extremes included), and a body weight of not less than 50 kg at screening.
3. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study, before any study-related procedures take place.
4. Must be healthy on the basis of physical examination, medical history, vital signs, and ECG performed at screening (results must be available on Day -1). If there are abnormalities the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.
5. Subject must be healthy on the basis of clinical laboratory test performed at screening (results must be available on Day -1). If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges (other than those listed in exclusion criterion 2), the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.
6. A woman (of childbearing potential) must have a negative highly sensitive serum betahuman chorionic gonadotropin pregnancy test, 4 days or less before dosing of
the first treatment period.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Has history or current clinically significant medical illness including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood

dyscrasias), lipid abnormalities, significant pulmonary disease (including bronchospastic respiratory disease), diabetes mellitus, hepatic or renal insufficiency (eg, estimated creatinine clearance below <90 mL/min at screening), gastrointestinal disease (such as significant diarrhea, gastric stasis, or constipation that in the investigator*s opinion could influence drug absorption or bioavailability), thyroid disease, neurologic or psychiatric disease, infection, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the study results.
2. Had one or more of the following laboratory abnormalities at screening as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events and in accordance with the normal ranges of the clinical laboratory:
- Serum creatinine Grade 1 or greater (>=1.1 x upper limit of laboratory normal range [ULN]) or creatinine clearance (using the CKD-EPI formula) <90 mL/min.
- Lipase Grade 1 or greater (>=1.1 x ULN), and/or total amylase Grade 2 or greater (>=1.5 x ULN).
- Hemoglobin (Hb) Grade 1 or greater (Female: <=7.2 mmol/L and Male: <=8.3 mmol/L).
- Platelet count Grade 1 or greater (<124.999 x 109/L).
- Absolute neutrophil count Grade 1 or greater (<=1.0 x 109/L).
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) Grade 1 or greater (>=1.25 x ULN).
- Total bilirubin Grade 2 or greater (>=1.6 x ULN).
- For proteinuria (spot urine) >=2+.
- Microscopic hematuria (>=5 red blood cells [RBC]/hpf); if a female subject is menstruating at the time of screening a urine retest is to be performed after the menstrual period.
- Any other laboratory abnormality of grade 2 or greater. For low-density lipoprotein (LDL) cholesterol values corresponding to DAIDS grade 2 or greater, subjects will not to be excluded as long as the value is not higher than ULN of the local lab.
3. Clinically significant abnormalities during physical examination, vital signs, or 12-lead electrocardiogram (ECG) at screening or at admission to the study center as deemed appropriate by the investigator.
4. With any history of clinically significant skin disease such as, but not limited to, dermatitis, eczema, drug rash, psoriasis, food allergy, or urticaria.
5. No medication, including over-the-counter products, systemic herbal medications or dietary supplements including products containing Hypericum perforatum (St. John*s wort) can be used at least 14 days (or longer, based on 5 times the elimination half-life) before the first intake of study drug (on Day 1 of the first treatment period) until collection of the last PK sample, except for paracetamol (acetaminophen) or ibuprofen, hormone replacement therapy in postmenopausal women, and hormone-based contraception.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-01-2020
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Descovy
Generic name:	emtricitabine/tenofovir alafenamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prezista
Generic name:	Darunavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Symtuza
Generic name:	(Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tybost
Generic name:	Cobicistat
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2020
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	EUCTR2019-002245-37-NL
CCMO	NL72334.056.19

Study results

Date completed: 05-05-2020

Results posted: 12-05-2021

Summary results
Trial ended prematurely

First publication
17-02-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File