Bioequivalence of Crushed Stribild with a normal breakfast or with drip feed compared to the whole tablet.

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Primary objective:To assess the bioequivalence of single dose STB after administration of standardized breakfast followed by a whole tablet (reference) and a crushed and suspended tablet (intervention I).To assess the bioequivalence of single dose...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON40850

Source
ToetsingOnline

Brief title
CRUSTRI

Condition

- Viral infectious disorders

Synonym
HIV

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bioequivalence, crushed, drip feed, stribild

Outcome measures

Primary outcome

The primary aim is to asses bioequivalence between the exposure to Elvitegravir, cobicistat, emtricitabine and Tenofovir disoproxil after dosing with a whole tablet (reference) versus a suspended tablet with a standardized breakfast (intervention I) or a bolus drip feed (intervention II).

Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic parameters AUC0-* and Cmax, and the Tmax, and T¬1/2 of intervention I (Standardized breakfast + suspended STB tablet) versus the reference treatment (Standardized breakfast + whole STB tablet).
Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic parameters AUC0-* and Cmax and Tmax and T¬1/2 of intervention II (Bolus drip feed + suspended tablet) versus the reference treatment (Standardized breakfast + whole STB tablet).

Secondary outcome

The secondary aim is to asses bioequivalence between the exposure to elvitegravir, cobicistat, emtricitabine and Tenofovir disoproxil after dosing with a suspended tablet with a standardized breakfast (intervention I) versus a bolus drip feed (intervention II).

Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic

parameters AUC0-*, Cmax,Tmax, T¬1/2 between intervention I (Standardized

breakfast + suspended STB tablet) versus intervention II (Bolus drip feed +

suspended tablet).

Study description

Background summary

Elvitegravir is an HIV-1 integrase inhibitor which is marketed in a fixed dose combination tablet with cobicistat, tenofovir and emtricitabine (Stribild®, referred to as STB). For patients with swallowing difficulties, administration of whole tablets can be problematic and tablets are cut or crushed to ease administration. In addition if HIV patients develop oppor-tunistic infections, patients can become severely ill and may end up on the intensive care. Patients at the intensive care might not be able to swallow medication. Therefore it is useful to know if it is possible to administer STB through a different route, like a feeding tube. If STB can be crushed or dissolved and given through a catheter it is also useful to know if it can be given with drip feed.

Currently there is no information about crushing STB tablets. *Crushing STB tablets into a liquid medium has not been studied and is not recom-mended* according to the SPC text. Depending on the biopharmaceutical characteristics of a drug formulation, crushing tablets can lead to altered pharmacokinetics of drugs. This has been shown for some of the antiretroviral drugs, such as ritonavir, lopinavir, efavirenz and tenofovir.

It is important to know whether pharmacokinetics are influenced by crush-ing of tablets as low concentrations are associated with virologic failure. Therefore higher doses might be needed. In addition, higher Cmax and/or exposure can lead to toxicity. As a result therapeutic drug monitoring is advised, or crushing the drug is a contra-indication based on the available data.
It has been shown that simultaneous oral ingestion of antacids and elvitegravir gives a decrease in Cmax and AUC of elvitegravir. This interac-tion is not shown for co-ingestion with omeprazole. Which makes it un-likely that this interaction is caused by a pH-lowering effect influencing the absorption of elvitegravir. It is probably a local gastrointestinal complexation phenomenon, similar to what has been observed with other HIV integrase inhibitors. A possible pharmacokinetic interaction between elvitegravir and complexation formers may be expected. Especially con-sidering the active binding sites of elvitegravir which bind magnesium metal ion cofactors. Although there is data that STB can be ingested with a protein rich drink, it is unclear if certain foods or liquids containing high amounts of

magnesium or other cations can cause this same interaction. [1, 2]

Therefore this study will be conducted to investigate whether crushed and suspended STB and crushed and suspended STB with drip feed are bioe-quivalent to taking STB as a whole.

Study objective

Primary objective:
To assess the bioequivalence of single dose STB after administration of standardized breakfast followed by a whole tablet (reference) and a crushed and suspended tablet (intervention I).
To assess the bioequivalence of single dose STB after administration of a standardized breakfast followed by a whole tablet (reference) and a standardized dose of drip feed followed by a crushed and suspended tablet (intervention II).
• To assess bioequivalence of the different administrations, the pharmacokinetics (AUC0-*, Cmax, Tmax, T¬1/2) of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxyl will be obtained and the geometric mean ratios of the AUC0-* and Cmax of the test versus reference treatment.

Secondary objective:
To assess the bioequivalence of single dose STB after administration of standardized breakfast followed by a crushed and suspended tablet (intervention I) versus administration of a standardized amount of drip feed followed by a crushed and suspended tablet (intervention II).
• To assess bioequivalence of the different ways of administration, the pharmacokinetics (AUC0-*, Cmax, Tmax, T¬1/2) of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxyl will be determined and the geometric mean ratios of the AUC0-* and Cmax of intervention I vs intervention II.

Tertiary objective:
To evaluate the safety and tolerability of co administration of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil in healthy subjects, after administration of whole and crushed STB.

Study design

Open-label, 3-period, randomized, cross-over, single-centre, phase-I, sin-gle dose trial in 24 healthy volunteers.

The 24 subjects will be divided into one of the following treatment se-quences: ABC; ACB; BCA; BAC; CAB; CBA

Treatment period:
A Standardized breakfast followed by STB (whole tablet).

B Standardized breakfast followed by crushed and suspended STB.
C 350 mL of drip feed (type) followed by crushed and suspended STB.

Between the different treatment periods a wash-out period of 7 days is scheduled.
On the day of administration, day 1, 7 and 14, a pharmacokinetic curve is recorded.

Intervention

See study design;
3 different administrations of one tablet of Stribild.

- breakfast + whole tablet
- breakfast + crushed and suspended tablet
- drip feed + crushed and suspended tablet

Study burden and risks

This study will be performed in healthy volunteers instead of HIV-infected patients. The study participants will not benefit from the participation in this clinical trial.
The most common adverse events are generally transient, self-limiting and mild-to moderate in severity. The most frequently reported adverse reactions were nausea (16%) and diarrhea (12%) [3].
Common adverse events of STB (>= 1 to <10% of the users): neutropenia, allergic reaction, hypophosphataemia, hyperglycaemia, hypertriglyceridaemia, decreased appetite, insomnia, abnormal dreams, headache, dizziness, diarrhea, vomiting, nausea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, abdominal pain, dyspepsia, constipation, abdominal distension, flatulence, increased transaminases, hyperbilirubinaemia1,rash,vesiculobullous rash, pustular rash, maculopapular rash, pruritus, urticaria, skin discolouration (increased pigmentation), elevated creatine kinase, increased blood creatinine, asthenia, pain and fatigue. See the Summary of Product Characteristics for complete information on all adverse reactions.
Participants will visit the clinical research centre for a screening visit , 6 short visits (10 minutes) and 3 full days (13 hours). The duration of the entire trial is 15 days. Duration of treatment with study medication is 3 days. For pharmacokinetic purposes 45 blood samples will be taken in total. For safety assessment (haematology and clinical chemistry), hCG bloodtest and blood glucose a total of 12 blood samples will be collected. The total bloodvolume taken will be approximately 423 mL. During the days that blood samples will be collected for a pharmacokinetic curve an intravenous cannula will be inserted to facilitate blood sampling and limit the amount of venous punctions.

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. Subject is at least 18 and not older than 55 years at screening.;2. Subject does not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to Day 1.;3. Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes included.;4. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.;5. Subject is in good age-appropriate health condition as established by medical history, physical examination, electrocardiography, results of biochemistry, haematology and urinalysis testing within 4 weeks prior to day 1. Results of biochemistry, haematology and urinalysis testing should be within the laboratory's reference ranges (see Appendix A). If laboratory results are not within the reference ranges, the subject is in-cluded on condition that the Investigator judges that the deviations are not clinically relevant. This should be clearly recorded.;6. Subject has a normal blood pressure and pulse rate, according to the Investigator's judgement.

Exclusion criteria

1. Creatinine clearance below 70mL/min.;2. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.;3. Positive HIV test.;4. Positive hepatitis B or C test.;5. Pregnant female (as confirmed by an hCG test performed less than 4 weeks before Day 1 or breast-feeding female. Female subjects of childbearing potential without adequate contraception, e.g. hysterec-tomy, bilateral tubal ligation, (non-hormonal) intrauterine device, total abstinence, double barrier methods, or two years post-menopausal. They must agree to take precautions in order to prevent a pregnancy throughout the entire conduct of the study.;6. Therapy with any drug (for two weeks preceding Day 1), except for acetaminophen.;7. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures and migraine), psychiatric disorders, gastro-intestinal disor-ders, renal and hepatic disorders, hormonal disorders (especially dia-betes mellitus), coagulation disorders.;8. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion. ;9. History of or current abuse of drugs, alcohol or solvents.;10. Inability to understand the nature and extent of the study and the pro-cedures required.;11. Participation in a drug study within 60 days prior to Day 1.;12. Donation of blood within 60 days prior to Day 1.;13. Febrile illness within 3 days before Day 1

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2015
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Stribild
Generic name:	elvitegravir, cobicistat, emtricitabine, tenofovir disoproxyl
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-10-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-11-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-003097-16-NL
CCMO	NL50771.091.14