Bioequivalence study of crushed Triumeq with or without drip feed compared to the whole tablet.

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Primary objectives:To assess the bioequivalence of a single-dose TRI as a whole tablet (reference) compared to a crushed and suspended tablet (intervention I).To assess the bioequivalence of a single-dose TRI as a whole tablet (reference) compared...

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

Summary

ID

NL-OMON42415

Source
ToetsingOnline

Brief title
SCRUM

Condition

- Viral infectious disorders

Synonym
HIV

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Bioequivalence, Crushed, Drip feed, Triumeq

Outcome measures

Primary outcome

The primary aim of this study is to assess the bioequivalence of dolutegravir, abacavir and lamivudine administered as a whole tablet (reference) compared to a crushed and suspended tablet in a fasted state (intervention I) or after a standardized amount of drip feed (intervention II).

Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic parameters AUC0-*, Cmax, and T* of intervention I compared to the reference treatment.

Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic parameters AUC0-*, Cmax, and T* of intervention II compared to the reference treatment.

Secondary outcome

The secondary aim of this study is to assess the bioequivalence of dolutegravir, abacavir and lamivudine after dosing as a crushed and suspended tablet in a fasted state (intervention I) compared to a crushed and suspended tablet after a standardized amount of drip feed (intervention II).

Geometric Mean Ratios and the 90% confidence interval of the pharmacokinetic parameters AUC0-*, Cmax, and T* of intervention I compared to intervention II.

Adverse events after administration of a single-dose TRI in the different

treatment arms will be described and compared (including clinically relevant

laboratory abnormalities).

Study description

Background summary

Dolutegravir is an HIV-1 integrase inhibitor which is marketed as a single tablet (Tivicay®) and in a fixed dose combination tablet with abacavir and lamivudine (Triumeq®, referred to as TRI). 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 opportunistic 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 TRI through a different route, like a feeding tube. If TRI 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 TRI tablets. 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 crushing of tablets as low concentrations are associated with virologic failure. Therefore higher doses or switching to other HIV-drugs 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 dolutegravir gives a decrease in Cmax and AUC of dolutegravir. This interaction is not shown for co-ingestion with omeprazole, which makes it unlikely that this interaction is caused by a pH-lowering effect influencing the absorption of dolutegravir. It is probably a local gastrointestinal complexation phenomenon, similar to what has been observed with other HIV integrase inhibitors. A possible pharmacokinetic interaction between dolutegravir and complexation formers may be expected. Especially considering the active binding sites of dolutegravir which bind magnesium metal ion cofactors. It is currently unclear if certain foods or liquids containing high amounts of magnesium or

other cations can cause this same interaction.

Therefore this study will be conducted to investigate whether crushed and suspended TRI and crushed and suspended TRI with drip feed are bioequivalent to taking TRI as a whole.

Study objective

Primary objectives:
To assess the bioequivalence of a single-dose TRI as a whole tablet (reference) compared to a crushed and suspended tablet (intervention I).
To assess the bioequivalence of a single-dose TRI as a whole tablet (reference) compared to 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*) of dolutegravir, abacavir, and lamivudine 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 a single-dose TRI as a crushed and suspended tablet (intervention I) compared to 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*) of dolutegravir, abacavir, and lamivudine will be obtained and the geometric mean ratios of the AUC0-* and Cmax of intervention I versus intervention II.

Tertiary objective:
To evaluate the safety and tolerability of co-administration of dolutegravir, abacavir and lamivudine in healthy adult subjects after administration of whole tablets and crushed and suspended tablets.

Study design

Open-label, 3 period, randomized, cross-over, single-center, phase I, single-dose study in 24 healthy adult subjects.

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

Treatment period:
• A: Single-dose TRI as a whole tablet in a fasted state
• B: Single-dose crushed and suspended TRI in a fasted state
• C: 250 ml drip feed (Nutrison) followed by a single-dose crushed and suspended TRI

Between the different treatment periods a wash-out period of 7 days is scheduled.

On the day of administration, day 1, 8 and 15, a pharmacokinetic curve is recorded.

Intervention

See study design.

3 different ways of administration of Triumeq:
- whole tablet
- crushed and suspended tablet
- standard amount of drip feed followed by a crushed and suspended tablet

Study burden and risks

The study participants are healthy adult subjects and will not benefit from the participation in this clinical trial.

Participants will visit the clinical research centre for a screening visit, 9 short visits, and 3 full days. The duration of the entire trial (excluding screening period) is 17 days. Duration of treatment with study medication is 3 days.

Triumeq has a good benefit/risk ratio. The most common adverse events are generally transient, self-limiting and mild-to moderate in severity. The most frequently reported adverse reactions in clinical trials of chronic use of Triumeq were nausea, insomnia, dizziness and headache.

For pharmacokinetic purposes 45 blood samples will be taken in total. For safety assessment (haematology and clinical chemistry), hCG blood tests and blood glucose, serology and pharmacogenetic testing, a total of 16 blood samples will be collected. The total blood volume taken will be approximately 330 ml. During the days that blood samples will be collected for a PK-curve, an intravenous cannula will be inserted to facilitate blood sampling and limit the amount of venous punctures.

Contacts

Public
Selecteer

Geert Grooteplein 10

Nijmegen 6525 GA
NL
Scientific
Selecteer

Geert Grooteplein 10
Nijmegen 6525 GA
NL

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 of age at the day of screening;
2. Subject weighs at least 40 kg;
3. Subject has a BMI of 18.5-30 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 four 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 included based on the Investigator*s judgment that the observed 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 judgment;
7. Subject does not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to day 1.

Exclusion criteria

1. Positive HIV test;
2. Positive hepatitis B or C test;
3. Positive HLA-B*5701 status;
4. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients;
5. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion;
6. Inability to understand the nature and extent of the study and the procedures required;
7. 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. hysterectomy, 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;
8. Therapy with any drug (including herbal remedies, multivitamins, magnesium- and calcium-containing supplements, etc.) (for two weeks preceding day 1), except for acetaminophen;
9. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures and migraine), psychiatric disorders, gastro-intestinal disorders, renal disorders (renal failure determined as an estimated Glomerular Filtration Rate (eGFR) below 50 ml/min (MDRD-based)), hepatic disorders (Child-Pugh B or C), hormonal disorders (especially diabetes mellitus), coagulation disorders;
10. History of or current abuse of drugs, alcohol or solvents;
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;
14. Co-worker of Radboud university medical center;

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):	04-04-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Triumeq
Generic name:	dolutegravir sodium, abacavir sulfate, lamivudine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-09-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-10-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-04-2016
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	EUCTR2015-002280-42-NL
CCMO	NL54232.091.15

Study results

Date completed:	22-04-2016
Actual enrolment:	22