Relative bioavailability study to investigate a potential interaction between dolutegravir (DTG) and tenofovir alafenamide fumarate/emtricitabine (F/TAF) administered as paediatric tablet formulations.

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Primary objectives:- To assess the relative bioavailability of TAF and TFV after a single-dose FTC/TAF 3x60/7.5 mg DT (reference TAF) compared to TAF and TFV after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30mg as...

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

Summary

ID

NL-OMON51616

Source
ToetsingOnline

Brief title
UNIVERSAL RBA

Condition

- Viral infectious disorders

Synonym
HIV

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Gilead,Gilead Sciences

Intervention

Keyword: bioavailability, dispersible, HIV, pharmacokinetics

Outcome measures

Primary outcome

The primary study parameters of this study are to assess:

- The relative bioavailability of TAF and TFV after a single-dose FTC/TAF 3x 60/7.5mg DT (reference TAF) compared to TAF and TFV after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30mg as 6 tablets of 5mg DT (test).

- The relative bioavailability of FTC after a single-dose FTC/TAF 3x 60/7.5mg DT (reference FTC) compared to FTC after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30 mg as 6 tablets of 5 mg DT (test).

- The relative bioavailability of DTG after a single-dose DTG 30mg as 6 tablets of 5mg DT (reference DTG) compared to DTG after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30mg as 6 tablets of 5mg DT (test).

- The relative bioavailability of the potential interaction, the pharmacokinetics (AUC0-*, Cmax, Tmax, T*) of DTG, FTC, TAF and TFV and the geometric mean ratios of the AUC0-tlast (TAF), AUC0-* (DTG, FTC and TFV) and

Cmax of the test versus reference treatment.

Secondary outcome

The safety and tolerability of (co-)administration of DTG, FTC/TAF in healthy

adult subjects.

Study description

Background summary

This is a study that will inform another project: UNIVERSAL. Within the UNIVERSAL project paediatric fixed dose combination tablets will be developed for children living with HIV, one of the products to be developed is a dispersible tablet (DT) combination of dolutegravir/tenofovir alafenamide fumarate/emtricitabine (DTG/FTC/TAF). In the UNIVERSAL 1 trial PK of existing DTG DT tablets and existing FTC/TAF DT tablets will be evaluated in children in the dose combinations suggested for the fixed dose tablet. The dose combinations will be evaluated by in silico modelling. If modelling project suggests dose strengths that are not approved, then new tablet strengths will be developed.
Potentially there is an interaction between DTG and TAF when given as dispersible tablets, based on experience with the bictegravir/FTC/TAF DT tablets developed by Gilead. A 30% increase in TAF exposure and a 31% increase in bictegravir (BIC) exposure was observed when combining these drugs in different fixed dose combinations. (1) BIC and DTG are similar in structure, which raises the question whether this may be the case between TAF and DTG as well.
Drug-drug-interaction studies with the adult film coated tablets DTG and FTC/TAF showed no effect of FTC/TAF on DTG, but 17% higher TAF and 25% higher tenofovir (TFV) concentrations in combination with DTG were observed. (2) These increases were not clinically relevant, but point in the same direction as FTC/TAF DT versus BIC/FTC/TAF DT.
Therefore, this study will be conducted to investigate whether there is a drug-drug-interaction between paediatric DTG 5 mg scored DT (30mg) and the 3x 60/7.5 mg FTC/TAF DT tablet. The dose is similar to the adult dose, because, a single tablet of the pediatric TAF/FTC tablet would generate almost unmeaserable TAF levels.

Study objective

Primary objectives:
- To assess the relative bioavailability of TAF and TFV after a single-dose

FTC/TAF 3x60/7.5 mg DT (reference TAF) compared to TAF and TFV after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30mg as 6 x 5 mg DT tablets (test).
- To assess the relative bioavailability of FTC after a single-dose FTC/TAF 60/7.5mg DT (reference FTC) compared to FTC after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30 mg as 6 x 5 mg DT tablets (test).
- To assess the relative bioavailability of DTG after a single-dose DTG 30mg as 6 x 5 mg DT tablets (reference DTG) compared to DTG after a single-dose FTC/TAF 3x 60/7.5mg DT in combination with a single dose of DTG 30mg as 6 x 5 mg DT tablets (test).
- To assess relative bioavailability of the potential interaction, the pharmacokinetics (AUC0-*, Cmax, Tmax, T*) of DTG, FTC, TAF and TFV will be obtained and the geometric mean ratios of the AUC0-tlast (TAF), AUC0-* (DTG, TFC and TFV) and Cmax of the test versus reference treatment.

Secondary objective:
- To evaluate the safety and tolerability of (co-)administration of DTG, FTC/TAF in healthy adult subjects.

Study design

Open-label, 3 period, randomized, cross-over, single-center, single-dose study in 16 healthy adult subjects.

Intervention

The 16 subjects will be divided into one of the following treatment sequences: ABC; ACB; BCA; BAC; CAB; CBA.

Treatment:
- A: Single-dose FTC/TAF 3x 60/7.5mg DT as a dispersed suspension in a fasted state
- B: Single-dose DTG 30mg as 6 x 5mg DT as a dispersed suspension in a fasted state
- C: Single-dose FTC/TAF 3x 60/7.5mg DT + DTG 30mg as 6 x 5mg DT as a co-dispersed suspension in a fasted state

Study burden and risks

This study will be conducted considering COVID-19 safety precaution for both staff and participants.
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 (10 minutes), and 3 full days (13 hours). The duration of the

entire trial (excluding screening period) is 17 days. Duration of treatment with study medication is 3 days (days 1, 8 and 15).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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. 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. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
4. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
5. Inability to understand the nature and extent of the study and the procedures required.
6. 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.
7. Therapy with any drug (including herbal remedies, multivitamins, iron supplements and calcium supplements) for two weeks preceding day 1, except for acetaminophen.
8. 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.
9. History of or current abuse of drugs, alcohol or solvents.
10. Participation in a drug study within 60 days prior to day 1.
11. Donation of blood within 60 days prior to day 1.
12. Febrile illness within 3 days before day 1.
13. 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):	02-11-2022
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Descovy
Generic name:	Emtricitabine / Tenofovir Alafenamide
Product type:	Medicine
Brand name:	Tivicay
Generic name:	Dolutegravir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-07-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-03-2023
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	EUCTR2021-005069-41-NL
CCMO	NL79111.091.22

Study results

Date completed:	24-03-2023
Actual enrolment:	16