A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection

Published: 14-09-2016
Last updated: 15-04-2024

The primary objective of this study is:- To assess the rates of HIV-1 infection in men who have sex with men (MSM) and transgender women (TGW) who have sex with men who are administered daily emtricitabine/tenofovir alafenamide (F/TAF) or...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON55726

Source
ToetsingOnline

Brief title
GS-US-412-2055

Condition

- Other condition

Synonym
HIV

Health condition

HIV preventie

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead

Intervention

Keyword: HIV-1, Transgender woman

Outcome measures

Primary outcome

The randomization for this study is a 1:1 ratio, which means that the subjects

chance of being assigned to Treatment Arm 1 (F/TAF) and Treatment Arm 2 (F/TDF,

(Truvada)) is equal. the subject will take two tablets daily. Everybody

participating in this study will get one active treatment.

Treatment Arm 1: F/TAF 200mg/25mg and placebo to match F/TDF

Treatment Arm 2: F/TDF 200mg/300mg and placebo to match F/TAF

Taking part in this study will last about 292 weeks, including the screening

visit.

During the first part of the study, which is called the double-blind phase, the subject will receive either F/TAF or F/TDF (Truvada) for at least 96 weeks. The exact duration of participation in the double-blind phase depends on when the subject enrolled in the study.

During the study, the subject will be required to visit the clinic at least 28 times over 292 weeks, including a 30-day follow-up visit at the end of the study.

Secondary outcome

3.1.2. Secondary Endpoints

The key (α-controlled) secondary endpoints in the blinded phase are:

•The percent change from baseline in hip BMD at Week 48 in a subset of subjects

•The percent change from baseline in spine BMD at Week 48 in a subset of subjects

•Assessment of renal biomarkers at Week 48

- percent change from baseline in urine beta-2-microglobulin to creatinine ratio

- percent change from baseline in urine RBP to creatinine ratio

- distribution of UP and UPCR categories

•The change from baseline in serum creatinine at Week 48

Other secondary endpoints include:

•The incidence of HIV-1 infection (as per Appendix 7) per 100 PY when all subjects have 96 weeks of follow-up after randomization

•The percent change from baseline in hip and spine BMD at Week 96 in the

blinded phase in a subset of subjects (not in the Netherlands)

•The change from baseline in serum creatinine at Week 96 in the blinded phase

•The incidence of treatment-emergent adverse events and laboratory toxicities

• Assessment of renal biomarkers at Week 96 in the blinded phase

- percent change from baseline in urine beta-2-microglobulin to creatinine ratio

- percent change from baseline in urine RBP to creatinine ratio

- distribution of UP and UPCR categories

•The change from baseline in serum creatinine at Week 96 in the blinded phase

•The incidence of treatment-emergent adverse events and laboratory toxicities

3.1.3. Other Endpoints of Interest

•The intracellular TFV-DP and FTC-TP trough concentrations (Ctrough) in PBMCs.

•The adherence rate using plasma FTC and/or TFV levels

•The incidence of HIV-1 infection per 100 PY at OL Week 48 for those who randomize to the F/TAF arm at baseline

•From the OL phase baseline to OL Week 48, percentage change in hip and spine BMD (in a subset of subjects), assessment of renal biomarkers (percent change in urine beta-2-microglobulin to creatinine ratio and urine RBP to creatinine ratio, distribution of UP and UPCR categories), and change from baseline in serum creatinine for those who switch to F/TAF from F/TDF in the OL phase

•The type and frequency of sexual practices that are associated with increased risk of HIV-1 infection

Study description

Background summary

The purpose of this study is to see if Emtricitabine and Tenofovir Alafenamide (F/TAF) is safe and effective for use as prevention of HIV-1 infection, also known as Pre Exposure Prophylaxis (PrEP) in healthy adults.

Study objective

The primary objective of this study is:
- To assess the rates of HIV-1 infection in men who have sex with men (MSM) and transgender women (TGW) who have sex with men who are administered daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization

The secondary objectives of this study are:
- To compare bone safety between the treatments as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine bone mineral density (BMD) in a subset of subjects at Week 48 and Week 96 in the blinded phase
- To compare renal safety between the treatments as determined by urine retinol-binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, urine protein to creatinine ratio (UPCR), and serum creatinine at Week 48 and Week 96 in the blinded phase
- To assess the rates of HIV-1 infection in MSM and TGW who have sex with men who are administered daily F/TAF or F/TDF when all subjects have 96 weeks of follow-up after randomization
- To compare the general safety between the treatments

Exploratory objectives of this study include:
- To evaluate the pharmacokinetics (PK) of intracellular tenofovir diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) in peripheral blood mononuclear cells (PBMCs)
- To assess the adherence rate using TFV-DP levels in dried blood spot (DBS) along with FTC and/or tenofovir (TFV) levels in plasma
- To evaluate the long term safety and rate of HIV-1 infections during the open label (OL) phase following the blinded phase for subjects who received F/TAF during the blinded phase
- To evaluate changes in renal and bone safety for those who switch to OL F/TAF from blinded F/TDF following the blinded phase
- To evaluate the type and frequency of sexual practices that are associated with increased risk of HIV-1 infection

Study design

Randomized, double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered orally once daily.

All subjects must meet all eligibility criteria in order to receive treatment in the study. Once randomized to receive treatment in the study, all subjects must return to the study center for required visits at Weeks 4, 12, and every 12 weeks thereafter.

All subjects will remain blinded to study treatment for at least 96 weeks. The primary endpoint data will be collected and analyzed when all subjects have a minimum follow up of 48 weeks and 50% of the subjects have 96 weeks of follow up after randomization.

Once all subjects have at least 96 weeks of follow up after randomization and upon notification by Gilead, all subjects will return to the study center for an end of blinded treatment phase visit (may coincide with their next scheduled visit).

Subjects who are still on blinded study drug at the end of blinded treatment phase visit will be offered entry into the OL phase of the study. Subjects who continue participation in the OL phase will be administered F/TAF once daily and will return to the study center for visits every 12 weeks up to OL Week 96. Subjects who have discontinued study drug prior to the end of blinded treatment phase visit due to HIV infection will be eligible to continue participation in the OL phase up to OL Week 48, but will not be administered F/TAF once daily. From OL Week 48 subjects who acquire HIV must complete the early study drug discontinuation (ESDD) visit and discontinue the study at the 30 Day Follow-up visit, 30 days after the last dose of study drug. Subjects who have discontinued study drug for any other reason prior to the end of blinded treatment phase visit will not be eligible to participate in the OL phase.

Subjects who remain on study at OL Week 96 will have the option to continue in the OL extension phase and attend study visits every 12 weeks through OL Week 144, after which the study will complete and subjects will transition to locally available HIV prevention services. Subjects who have been diagnosed and confirmed as HIV positive during this phase must complete the ESDD visit and discontinue the study at the 30-Day Follow Up visit, 30 days after the last dose of study drug.

During the blinded treatment phase, subjects may choose to continue to participate in the study without taking study drug (*on-study, off-study drug*). Subjects who permanently discontinue study drug and continue to attend normal study visits (at minimum one visit at least 30 days after last dose) are not required to complete the follow-up visit. Any subject who has an ESDD visit

and who will not continue participating in the study, or any subject who will not continue participation in the OL phase of the study, must complete the 30-Day Follow-Up visit 30 days after the last dose of study drug.

DXA scans will be performed during regular intervals throughout the study (blinded and OL phase) in a subset of approximately 400 subjects at a subset of sites (excluding Germany).

Study burden and risks

During the study, you will be required to visit the clinic at least 28 times over 292 weeks, including a 30-day follow-up visit at the end of the study. Burden, -questionnaires blood drawn at every visit. Swab samples from mouth and rectum.

Collecting blood samples. The collection of these samples may cause pain, bruising, lightheadedness, fainting, and very rarely, infection at the site of the needle stick.

See appendix 2&3 Protocol amendment 6 dd 10Nov2020.

The study may provide extra knowledge and information regarding preventing HIV-1

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) HIV-1 negative status
2) MSM or TGW (male at birth) who have at least one of the following:
a) condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)
b) documented history of syphilis in the past 24 weeks
c) documented history of rectal gonorrhea or chlamydia in the past 24 weeks
3) Age >= 18 years
4) Estimated GFR >= 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance
5) Adequate liver and hematologic function
6) Willing and able to comply with study procedures

Exclusion criteria

1) Known hypersensitivity to the IMP, the metabolites, or formulation excipient
2) Have a suspected or known active, serious infection(s)
3) Acute viral hepatitis A, B or C or evidence of chronic hepatitis B infection. Subjects found to be susceptible to HBV infection should be referred for HBV vaccination. Subjects found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.
4) Need for continued use of any contraindicated concomitant medications
5) Have an implanted defibrillator or pacemaker
6) Have a history of osteoporosis or bone fragility fractures
7) Current alcohol or substance abuse judged by the Investigator to be problematic such that it potentially interferes with subject study compliance

8) Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable
9) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements
10) Have received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening.
11) Participation in any other clinical trail (including observational trails) without prior approval from the sponsor is prohibited while participating in this trial.

Study design

Design

Study phase:	3
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-04-2017
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	F/TAF
Generic name:	F/TAF
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	F/TDF
Generic name:	Truvada
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-001399-31-NL
CCMO	NL58586.018.16