A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

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The primary objective of this study is:- To evaluate the effect of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single-tablet regimen (STR) on renal parameters at Week 24The secondary objectives of this study are:- To...

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

Summary

ID

NL-OMON41597

Source
ToetsingOnline

Brief title
GS-US-292-0112

Condition

- Viral infectious disorders
- Renal disorders (excl nephropathies)

Synonym
Human Immunodeficiency virus (HIV-1) infections, renal impairment

Research involving
Human

Sponsors and support

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

Intervention

Keyword: HIV-1, Renal impairment, Single tablet regimen

Outcome measures

Primary outcome

Safety:

Renal safety will be monitored by evaluating serum chemistries, GFR, urinalysis, and other markers of potential tubular injury, including graded renal lab abnormalities (serum creatinine, serum phosphorus, serum potassium, serum bicarbonate, proteinuria, and normoglycemic glycosuria). Bone safety will be monitored by evaluating DEXA scans of the spine and hip.
Safety evaluations will also include reporting of adverse events, clinical laboratory tests, physical examinations, and vital signs.

Efficacy:

Virologic response will be determined using the percentages of subjects with HIV-1 RNA < 50 copies/mL (FDA Snapshot analysis).

PK/PD:

The PK of EVG, COBI, FTC, TAF, and TFV and the PD endpoint will be evaluated for subjects enrolled in PK/PD substudy. Additionally, at substudy sites that can perform PBMC processing, tenofovir diphosphate (TFV-DP) concentrations in

PBMCs will be determined and pharmacokinetics explored.

Secondary outcome

See primary parameters/ outcome

Study description

Background summary

The treatment of HIV infection requires the combination of several medications in order to decrease the amount of virus in the body, improve immune function and delay the progression of the disease. This has generally required patients to take a large number of pills each day, and many experience a loss of effectiveness of their current medication regimen over time or unacceptable side effects. Therefore, it is important to develop new drug regimens. In addition, the combination of drugs into a single tablet reduces the number of pills a patient has to take and makes it more convenient to stick to the prescribed drug regimen.

This study will be performed in HIV- positive patients with mild to moderate renal impairment. Patients with HIV are at risk for HIV- associated development of acute and chronic kidney disease. The majority of currently available medications are prescribed as fixed dose combinations, HIV-positive patients with chronic kidney disease have particularly limited therapeutic options. The availability of a single tablet regimen composed of potent agents with improved tolerability and long-term safety, that does not require dose adjustments at eGFR <50, would represent an important therapeutic innovation.

The safety and how well these drug combinations are tolerated will be determined based on physical exams, laboratory tests, bone scans and questions about any problems you might experience during the study.

Study objective

The primary objective of this study is:
- To evaluate the effect of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single-tablet regimen (STR) on renal parameters at Week 24

The secondary objectives of this study are:
- To evaluate the effect of the E/C/F/TAF STR on renal parameters at Weeks 48, 96 and 144
- To measure the proportion of subjects achieving virologic response (HIV-1 RNA

< 50 copies/mL, FDA snapshot analysis) at Weeks 24, 48, 96 and 144
- To evaluate the safety and tolerability of the E/C/F/TAF STR through 144 weeks of treatment

Study design

Open-label, multicenter, multi-cohort study to assess the safety, tolerability, and efficacy of a STR of E/C/F/TAF in HIV-positive, adult subjects with mild to moderate renal impairment.

Subjects will be enrolled into one of the following two cohorts:
Cohort 1: Treatment-experienced, eGFRCG 30-69 mL/min
Cohort 2: Treatment-naïve, eGFRCG 30-69 mL/min

Estimated glomerular filtration rate (eGFR) will be measured by the Cockroft-Gault formula (eGFRCG).

Intervention

Single-tablet regimen (STR) of elvitegravir 150mg/cobicistat

150mg/emtricitabine 200mg/tenofovir alafenamide 10mg administered orally once daily with food.

Study burden and risks

For a complete overview of all study procedures Please refer to the protocol and patientinformation leaflet. All risks are described in there.

As of November 2012, 112 HIV-positive subjects have been dosed with the E/C/F/TAF combination pill as part of a Phase 2 study to evaluate the drug*s safety and ability to suppress HIV viral load to undetectable levels (efficacy). After 6 months of therapy, 87% of subjects had undetectable viral loads (HIV-1 RNA < 50 copies/mL). Treatment was generally well tolerated as most AEs were mild and not associated with treatment discontinuation. No new or unexpected adverse events occurred. Subjects taking E/C/F/TAF had smaller changes in markers of kidney function and bone mineral density than subjects on a TDF-based regimen. The differences were statistically significant and may have important clinical relevance for individual patients. The frequency and type of adverse events and laboratory abnormalities was comparable to the TDF-based regimen.

In addition, more than 100 HIV-negative subjects have been dosed with the E/C/F/TAF combination pill as part of a Phase 1 study to evaluate the level of each drug in the blood (pharmacokinetics). No deaths or serious side effects occurred during the study. One subject discontinued from the study because of a

nonserious adverse event of increased creatinine phosphokinase (CPK) levels in the blood that was assessed as related to study drug. The most frequently reported side effect was constipation. Other side effects included nausea, dizziness, headache, breast tenderness, and papular rash. No subject in any treatment arm developed any clinically significant abnormalities on ECG throughout the study.

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

* The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
* CD4+ count of >50 cells/*L
* Stable renal function: serum creatinine measurements to be taken at least once (within

three months of screening). Measurements difference versus screening value must be <25% of the screening value
* Cause of underlying chronic kidney disease (eg hypertension, diabetes) stable, without change in medical management, for 3 months prior to baseline
* Normal ECG (or if abnormal, determined by the Investigator to be not clinically significant)
* Hepatic transaminases (AST and ALT) * 5 x upper limit of normal (ULN)
* Total bilirubin * 1.5 mg/dL, or normal direct bilirubin (subjects with documented Gilbert*s Syndrome or hyperbilirubinemia due to atazanavir therapy may have total bilirubin up to 5 x ULN).
* Adequate hematologic function (absolute neutrophil count * 1,000/mm3; platelets * 50,000/mm3; hemoglobin * 8.5 g/dL)
* Serum amylase * 5 x ULN (subjects with serum amylase > 5 x ULN will remain eligible if serum lipase is * 5 x ULN)
* Females of childbearing potential (as defined in Section *7.8) must agree to utilize highly effective contraception methods (two separate forms of contraception, one of which must be an effective barrier method, or be non-heterosexually active, practice sexual abstinence or have a vasectomized partner) from screening throughout the duration of study treatment and for 30 days following the last dose of study drug.
* Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing
* Male subjects must agree to utilize a highly effective method of contraception during heterosexual intercourse throughout the study period and for 30 days following discontinuation of investigational medicinal product. A highly effective method of contraception is defined as two separate forms of contraception, one of which must be an effective barrier method, or male subjects must be non-heterosexually active, or practice sexual abstinence.
* Age * 18 years

Exclusion criteria

* A new AIDS defining condition (excluding CD4 cell count and percentage criteria) diagnosed within the 30 days prior to screening,with the exception of the first two bullet points (refer to Appendix 6)
* HCV antibody positive. Subjects who are HCV positive, but have a documented negative HCV RNA, are eligible
* Hepatitis B surface antigen (HBVsAg) positive
* Subjects receiving drug treatment for Hepatitis C, or subjects who are anticipated to receive treatment for Hepatitis C during the course of the study
* Subjects experiencing decompensated cirrhosis (e.g., ascites, encephalopathy, etc.)
* Females who are breastfeeding
* Positive serum pregnancy test (female of childbearing potential)
* Have an implanted defibrillator or pacemaker
* Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance
* A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy

other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Baseline and must not be anticipated to require systemic therapy during the study.
* Active, serious infections (other than HIV 1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Baseline
* Subjects on hemodialysis, other forms of renal replacement therapy, or on treatment for underlying kidney diseases (including prednisolone, and dexamethasone)
* Subjects receiving ongoing therapy with any of the medications in the table below, including drugs not to be used with EVG, COBI, FTC, or TAF (refer to the individual agents Prescribing Information); or subjects with any known allergies to the excipients of E/C/F/TAF STR

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2013
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	E/C/F/TAF
Generic name:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide tablet

Ethics review

Approved WMO Date:	24-06-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-09-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	01-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

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	EUCTR2013-000516-25-NL
ClinicalTrials.gov	NCT01818596
CCMO	NL45016.100.13