Multicenter, Double-Blind, Randomized, 2-Part, Dose Ranging Study to Compare the Safety, and Antiretroviral Activity of MK-1439 Plus TRUVADA® Versus Efavirenz Plus TRUVADA® in Antiretroviral Treatment-Naïve, HIV-1 Infected Patients

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MK-1439 is a promising NNRTI to be used in combination with other antiretrovirals (ARTs) for the treatment of HIV infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and most common NNRTI...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON41652

Source
ToetsingOnline

Brief title
MK-1439 plus TRUVADA vs Efavirenz plus TRUVADA in HIV-1 Patients

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym

HIV, Infection with the Human Immunodeficiency Virus

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme Corp.;(een dochteronderneming van Merck & Co. Inc.)

Intervention

Keyword: Antiretroviral Treatment-Naïve, HIV, MK-1439, Phase 2

Outcome measures

Primary outcome

The primary endpoints are the proportion of patients achieving HIV RNA <40 copies/mL at Week 24, and the safety and tolerability of MK-1439 compared with efavirenz when each is given in combination with TRUVADA® through Week 24. A single dose will be selected for further study after all patients complete the Week 24 visit in Part I. Each site will receive an administrative letter communicating the selected dose, then patients on other doses of MK-1439 will be switched to the selected dose at the next planned study visit while maintaining the study blind. Secondarily, longer-term safety and efficacy data will be evaluated at Week 48 and Week 96.

Secondary outcome

Please refer to protocol section 3.5.3: Analysis Endpoints, page 49 -51

Study description

Background summary

This is a Multicenter, Double-Blind, Randomized, 2-Part, Dose Ranging Study to Compare the Safety, and Antiretroviral Activity of MK-1439 Plus TRUVADA® Versus Efavirenz Plus TRUVADA® in Antiretroviral Treatment-Naïve, HIV-1 Infected Patients.

MK-1439 is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) being studied for treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral naïve HIV-infected patients.

Study objective

MK-1439 is a promising NNRTI to be used in combination with other antiretrovirals (ARTs) for the treatment of HIV infection. It is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and most common NNRTI resistant variants at concentrations achieved with once daily dosing. It is anticipated that MK-1439 will be efficacious in combination with other ARTs in treatment naïve patients.
Currently efavirenz is the preferred NNRTI for initial treatment, and in a fixed dose regimen (FDR) (ATRIPLA®) is the leading anchor agent in HIV treatment. This compound has demonstrated potent viral suppression, but has limitations of central nervous system (CNS) adverse experiences and also has teratogenic potential. MK-1439 should have a more favorable CNS profile and therefore, may result in improved patient tolerability and adherence. MK-1439 is also not expected to have issues of teratogenicity.
MK-1439 is intended for use in the treatment-naïve population, in whom rates of transmitted NNRTI resistance are low, but is also expected to be active against several common efavirenz resistance mutations, specifically K103N and Y181C.
The 25 mg dose is expected to achieve target pharmacokinetic (PK) values, specifically C24hr (concentration in 24 hours) of 54 nM, and the additional doses of 50, 100 and 200 mg will explore the safety and efficacy of MK-1439 with increased exposure. Based on Phase I safety, pharmacokinetic and Phase Ib efficacy results, all doses selected for this study should be well tolerated, safe and confer adequate antiviral effect.
These doses have been selected so as to minimize the overlap of exposures between doses. As all patients enrolled in this study should harbor only wild-type virus, the lowest dose selected (25 mg) is projected to supply an ample efficacy margin for antiretroviral activity with > 95% of patients achieving a C24hr on Day 1 of ~ 4.2-fold greater than the wild-type virus target (80.7 nM vs. 19 nM). Some accumulation is anticipated with achievement of pharmacokinetic steady state on Day 3 to 5 and commensurate elevations in AUC0-24hr (Area Under the Curve), Cmax, (maximum concentration)and C24hr of approximately 1.2 to 1.5-fold as compared to first dose.
Factors that impact treatment success include efficacy/barrier to resistance, safety and tolerability, simplicity/convenience of administration and drug-drug interactions. There is a clear medical need for new regimens and strategies that are highly effective, have high barrier to resistance development, are very well tolerated, and are simple to administer, which will promote increased

adherence and decrease treatment fatigue. This need is further driven by the necessity for life-long treatment of HIV infection including in patients who are older and who have co-morbid diseases/conditions.

Study design

This is a multicenter, double-blind (with in-house blinding), randomized, 2-part dose ranging study in ~ 320 ART-naïve HIV infected patients (~200 patients to enroll in Part I and ~120 in part II). All patients will be stratified by their initial (Screening) HIV RNA (* or > 100,000 copies/mL).
Part I will examine the safety, tolerability, pharmacokinetics, and efficacy of 4 once-daily (q.d.) doses of MK-1439 (25 mg, 50 mg, 100 mg, and 200 mg.) versus once-daily efavirenz (600 mg q.h.s), each in combination with once daily TRUVADA® (emtricitabine 200 mg (+) tenofovir disoproxil fumarate 300 mg) for at least 24 weeks in ~200 patients. Patients will be randomized to 1 of the 5 treatment arms (Groups 1 to 5) in 1:1:1:1:1 ratio (~40 per treatment group).
The primary endpoints are the proportion of patients achieving HIV RNA <40 copies/mL at Week 24, and the safety and tolerability of MK-1439 compared with efavirenz when each is given in combination with TRUVADA® through Week 24. A single dose will be selected for further study after all patients complete the Week 24 visit in Part I. Each site will receive an administrative letter communicating the selected dose, then patients on other doses of MK-1439 will be switched to the selected dose at the next planned study visit while maintaining the study blind. Secondarily, longer-term safety and efficacy data will be evaluated at Week 48 and Week 96.
Part II will be initiated after the MK-1439 dose has been selected as described above. About 120 additional patients will be randomized in 1:1 ratio to the selected dose of MK-1439 or efavirenz (600 mg q.h.s.), each in combination with TRUVADA® for 96 weeks of blinded treatment. All study therapy will be administered once daily. The purpose of enrolling additional patients in Part II is to provide sufficient safety data at the selected dose of MK-1439 for comparison with efavirenz, particularly with regard to selected CNS events.
See Figure 1-1 for a description of the study flow. The study will remain blinded until all patients complete their final visit.

Patients participating in the dose ranging pat of the study will receive MK-1439 (or placebo) in Bottles A, B, C, and D. After dose selection, all patients will receive MK-1439 (or placebo) in Bottles G, or G and H (this includes patients continuing from Part I after dose selection, and those randomized to Part II).
An administrative letter will be sent to the sites at the time of dose selection, after which patients in Part I will be switched to the selected dose and Part II will be initiated. This letter will inform the sites whether to instruct patients to dose from Bottle G only (if 25 mg or 100 mg q.d. is the final selected dose of MK-1439), or from both Bottle G and Bottle H (if 50 mg or 200 mg q.d. is the final selected dose of MK-1439). Through the entire study (Parts I and II), patients will receive efavirenz (or placebo) in Bottle

E and TRUVADA® (open label) in Bottle F.
Part I: Patients will be randomized to 1 of the 5 treatment arms (Groups 1 to 5) in 1:1:1:1:1 ratio to the following treatments: MK-1439 25 mg q.d., MK-1439 50 mg q.d., MK-1439 100 mg q.d., MK-1439 200 mg q.d., or efavirenz 600 mg q.h.s., each in combination with TRUVADA®. The different doses of MK-1439 and efavirenz will be administered in a treatment-blinded fashion, while TRUVADA® will be administered in an open-label fashion (see Table 1-1). Treatment at these doses will be given for at least 24 weeks. When the dose of MK-1439 is chosen after all patients reach the Week 24 analysis, patients on other doses of MK-1439 will be switched to the selected dose of MK-1439 (see Table 1-2) at their next planned visit while maintaining the blind, and all patients will continue blinded treatment until Week 96.
Part II: An additional 120 patients will be randomized in a 1:1 ratio to the selected dose of MK-1439 or efavirenz (at 600 mg q.h.s.), each in combination with TRUVADA®. As in Part I, the chosen dose of MK-1439 and efavirenz will be administered in a treatment-blinded fashion, while TRUVADA® will be administered in an open-label fashion (see Table 1-2). Treatment will be given for 96 weeks.
In both Part I and Part II, each study therapy will be administered once daily as follows:
Morning
* MK-1439 (or placebo) should be taken in the morning and can be taken without regard to food.
* Open label TRUVADA® is to be taken with food in the morning. This should generally be taken together with the dose of MK-1439 (or placebo).
Bedtime
* Efavirenz (or placebo) is to be taken at bedtime and should be taken without food on an empty stomach.

Intervention

not applicable

Study burden and risks

Bijwerkingen: uit het ICF kopieren.

Contacts

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US
Scientific
Merck Sharp & Dohme (MSD)

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New Jersey NJ 08889-0100
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

a. Patient is a male or female of at least 18 years of age on the day of signing the informed consent. Patient provides written informed consent for the trial. The patient will also provide consent for Future Biomedical Research; however, the patient may participate in the main trial without participating in Future Biomedical Research.;b. Patient is HIV positive as determined by a positive ELISA and has screening plasma HIV RNA (completed by the central laboratory) * 1,000 copies/mL within 45 days prior to the treatment phase of this study.;c. Patient has a screening CD4 cell count *100 cells/mm3(completed by the central laboratory) within 45 days prior to the treatment phase of this study.;d. Patient is naïve to antiretroviral therapy (ART).;e. Patient has had the following laboratory values within 45 days prior to the treatment phase of this study:;1) Serum creatinine within normal limits.;2) INR *1.2;3) Urinalysis within normal limits.;Note: Clinically insignificant abnormalities on urinalysis may be permitted after retest, provided these are documented as clinically insignificant per investigator.;4) Hemoglobin *9.0 g/dL (if female) or *10.0 g/dL (if male).;5) Absolute neutrophil count *1000/mm3.;6) Platelet count *100,000/ mm3.;7) Total serum bilirubin less than or equal to the upper limit of normal.;8) Alkaline phosphatase <1.5 x upper limit of normal.;9) AST (SGOT) and ALT (SGPT) <1.5 x upper limit of normal.;f. In the opinion of the investigator, the patient should be considered clinically stable with no signs or symptoms of acute infection, at the time of entry into the study; i.e., clinical status and all chronic medications should be unchanged for at least 2 weeks prior to the start of treatment in this study.;g. Patient who is of reproductive potential agrees to remain abstinent or use (or have

their partner use) 2 acceptable methods of birth control throughout the study and for 12 weeks post study. Acceptable methods of birth control are: oral contraceptives, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, and vasectomy.;OR;Patient who is not of reproductive potential1, is not sexually active, whose current partner(s) is not of reproductive potential, or whose sexual activity is exclusively homosexual is eligible without requiring the use of contraception.

Exclusion criteria

a. Male patient is planning to impregnate or provide sperm donation for the duration of the study plus an additional 12 weeks. Female patient is pregnant or breast-feeding, or expecting to conceive or donate eggs for the duration of the study plus an additional 12 weeks.;b. Patient has received any approved or experimental antiretroviral agents or is anticipated to receive such medications (beyond those outlined as study medication in this protocol) during the course of the study.;c. Patient has used any immunomodulators or immunosuppressive therapy within one month prior to treatment in this study. Short courses of corticosteroids (e.g., as for asthma exacerbation) are allowed.;d. Patient requires or is anticipated to require any of the prohibited medications noted in Section 3.2.1.;e. Patient has been treated for a viral infection other than HIV, such as hepatitis B, with an agent that is active against HIV including but not limited to adefovir, tenofovir disoproxil fumarate, lamivudine, emtricitabine, or entecavir.;Note: Patients may be enrolled if treatment occurred prior to the diagnosis of HIV.;f. Patient has significant hypersensitivity or other contraindication to any of the components of the study drugs (emtricitabine, tenofovir disoproxil fumarate, and/or efavirenz).;g. Patient has documented or known HIV resistance to emtricitabine, tenofovir disoproxil fumarate, and/or efavirenz, based on genotypic resistance analysis.;h. Patient has a history of renal or urinary obstructive disease, requires dialysis (hemodialysis, continuous ambulatory peritoneal dialysis [CAPD], or other forms of dialysis), or has a calculated creatinine clearance at time of screening of *80 mL/min, based on the Cockcroft-Gault equation which is as follows (and 0.85 times this value for females):;Clcr (mL/min) = (140*age) x weight (in kg)____;72 x serum creatinine (mg/dL);i. Patient with active Hepatitis C virus (HCV) co-infection (defined as detectable HCV RNA) or Hepatitis B virus (HBV) co-infection (defined as HBsAg positive). Patients with prior/inactive HCV infection (defined as undetectable HCV RNA) or past HBV infection (defined as HBsAg negative and HBsAb positive) may be enrolled.;j. Patient has a history of alcohol or other substance abuse which in the opinion of the investigator would interfere with patient compliance or safety.;k. Patient has any condition or prestudy laboratory abnormality, or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the patient.;l. Patient has participated in a study with an investigational compound/device within one month of signing informed consent or is anticipating to participate in such a study involving an investigational compound/device during the course of this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-05-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MK-1439
Product type:	Medicine
Brand name:	SUSTIVA
Generic name:	efavirenz
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2012-001573-93-NL
ClinicalTrials.gov	NCT01632345
CCMO	NL41478.078.12