A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA* Once-Daily in Treatment-Naïve HIV-1 Infected Subjects

Published: 12-06-2015
Last updated: 19-04-2024

The primary objectives are:In HIV-1 positive, treatment-naive subjects with pre-treatment HIV RNA * 1,000 copies/mL:1) To evaluate the non-inferior antiretroviral activity of MK-1439A q.d. compared to ATRIPLA q.d. as measured by the proportion of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON42331

Source
ToetsingOnline

Brief title
MK-1439A versus ATRIPLA in treatment-naïve HIV-1 infected subjects

Condition

- Viral infectious disorders

Synonym
HIV-1-infection

Research involving

Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: industrie

Intervention

Keyword: ATRIPLA, HIV-1, MK1439A

Outcome measures

Primary outcome

The primary efficacy parameter in the study is viral load as measured by HIV-1 RNA, which is consistent with other clinical trials in HIV-infected patients and the current regulatory guidance.

The primary safety endpoint in this study is the proportion of subjects with neuropsychiatric AEs by Week 48 in three categories; dizziness, sleep disorders, and altered sensorium (for example, depressed level of consciousness, lethargy, somnolence, syncope).

Secondary outcome

Secondary and exploratory measurements for efficacy include HIV RNA < 40 copies/mL (the lower limit of quantification of the Abbott RealTime HIV-1 Assay), HIV RNA <200 copies/mL, change from baseline in CD4 cell counts, PK/PD analysis for MK1439, time to loss of virologic response (TLOVR), and viral resistance for subjects who meet protocol defined virologic failure criteria and whose virus can be amplified.

Secondary and exploratory measurements for safety include clinical and laboratory adverse experiences, change from baseline in fasting serum lipids, time to discontinuation due to an adverse experience and predefined limits of change in laboratory parameters.

Study description

Background summary

HIV infection, which causes Acquired Immune Deficiency Syndrome (AIDS) and for many years was associated with substantial morbidity and mortality, has now become a chronic disease that can be controlled through life-long combination antiretroviral therapy (ART) or Highly Active Antiretroviral Therapy (HAART). While HAART can delay disease progression and death, as well as reduce the risk of HIV transmission, it does not cure the infection. As a result, lifelong treatment must be maintained, which may lead to therapy fatigue and intolerable side-effects. Additionally, there is currently still significant concern regarding toxicities of some widely-used antiretroviral agents.

Currently, efavirenz is the preferred NNRTI for first-line therapy of treatment-naïve HIV-infected subjects. ATRIPLA* consists of efavirenz 600 mg + emtricitabine 200 mg + TDF 300 mg, and is the leading agent in HIV treatment. Efavirenz has demonstrated potent viral suppression but is associated with an increased risk of neuropsychiatric adverse experiences (AEs; especially dizziness and sleep disorders) and lipid abnormalities relative to other therapies. Efavirenz is also a perpetrator of numerous drug-drug interactions and, thus, may have limitations for use in aging patients who have an increased likelihood of using concomitant mediations.

MK-1439 is a novel NNRTI being studied for the treatment of HIV-1 infection in antiretroviral-naïve HIV-infected subjects. MK-1439 is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and the most common NNRTI resistant variants at concentrations achieved with once daily dosing. Furthermore, the available data from a Phase 2 study in treatment-naive HIV-infected patients demonstrate that MK-1439 in combination with TDF/emtricitabine has a favorable safety and tolerability profile and potent efficacy, with ~76% of patients receiving MK-1439 achieving undetectable viral load.

Study objective

The primary objectives are:

In HIV-1 positive, treatment-naive subjects with pre-treatment HIV RNA * 1,000 copies/mL:

1) To evaluate the non-inferior antiretroviral activity of MK-1439A q.d. compared to ATRIPLA q.d. as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48.

2) To evaluate the safety and tolerability of MK-1439A q.d. compared with ATRIPLA* q.d. as measured by the proportion of subjects with neuropsychiatric adverse events in the following categories:
* Dizziness
* Sleep disorders and disturbances
* Altered Sensorium

(see protocol section 3.2 for all secundary objectives)

Study design

This is a multicenter, double-blind, randomized, active-controlled trial to evaluate the safety and efficacy of MK-1439A once-daily (q.d.) compared with ATRIPLA* q.d. in antiretroviral treatment-naïve subjects with human immunodeficiency virus type 1 (HIV-1) infection. There will be 14 visits over a period of approximately 2 years.

Intervention

Patients receive 2 bottles of study medication (labeled A and B) and take 1 tablet each day from both bottles.

Bottle A (MK-1439A or placebo): 1 tablet every day at the same time, regardless of food intake
Bottle B (ATRIPLA* or placebo):1 tablet every day at bedtime, on an empty stomach

Study burden and risks

Patients take study medication once daily during approx. 2 years, and visit the study doctor every 4-8 weeks until week 36, and every 12 weeks thereafter.

During the visits, the following activities are done: physical exam, collection of blood and urine samples, ECG (Visit 2 only), and the patient will be asked to complete a questionnaire (Work Productivity and Activity Impairment Questionnaire (WPAI)).

The patient may experience physical and/or psychological discomfort during the study activities (e.g. blood sampling, ECG).

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

See section 5.1.2 of the protocol.;1.be at least 18 years of age on the day of signing the informed consent;
2.understand the study procedures and voluntarily agree to participate by giving written informed consent (or have a legal representative provide written informed consent) for the trial. The subject or his/her legal representative may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3.be HIV-1 positive as determined by a positive result on an enzyme-immunoassay, have

screening plasma HIV-1 RNA (determined by the central laboratory) *1000 copies/mL within 45 days prior to the treatment phase of this study, and have HIV treatment indicated based on physician assessment. Local treatment guidelines should be considered in the decision to initiate therapy.
4.be naïve to antiretroviral therapy (ART) including investigational antiretroviral agents.;5.have the following laboratory values at screening within 45 days prior to the treatment phase of this study: a) Alkaline phosphatase *3.0 x upper limit of normal b)AST (SGOT) and ALT (SGPT) *5.0 x upper limit of normal c) Hemoglobin *9.0 g/dL (if female) or *10.0 g/dL (if male). Calculated creatinine clearance at the time of screening * 50 mL/min.
6.clinically stable with no signs or symptoms of active infection at the time of entry into the study.
7.be highly unlikely to become pregnant or to impregnate a partner.

Exclusion criteria

See section 5.1.3 of the protocol.;1.has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study or interfere with the subject*s participation for the full duration of the study, such that it is not in the best interest of the subject to participate.
2.is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history of drug or alcohol abuse or dependence. The nature and potential clinical context of the subject's illicit drug use, in relation to their exclusion from this trial, will be at the discretion of the Investigator.
3.has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, adefovir, tenofovir, entecavir, emtricitabine, or lamivudine.
4.has documented or known resistance to study drugs including MK-1439, efavirenz, emtricitabine, lamivudine, and/or tenofovir, as defined below: ;a.Resistance to MK-1439 or efavirenz for the purpose of this study includes the following NNRTI mutations: L100I, K101E, K101P, K103N, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, G190A, G190S, H221Y, L234I, P225H, F227C, F227L, F227V, M230L, M230I;b.Resistance to emtricitabine, lamivudine and tenofovir includes the following mutations: K65R, M41L, T69S (insertion complex), Q151M, M184I, M184V, L210W, T215F, T215Y, K219E, K219Q, D67N, K70R and K70E. ;5.has participated in a study with an investigational compound/device within 30 days prior to signing informed consent or anticipates participating in such a study involving an investigational compound/device during the course of this study.;6.has used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study. ;Note: Short courses of corticosteroids (e.g., as for asthma exacerbation) will be allowed.;7.requires or is anticipated to require any of the prohibited medications noted in the protocol.;8.has significant hypersensitivity or other contraindication to any of the components of the study drugs as determined by the investigator.;9.has a current (active) diagnosis of acute hepatitis due to any cause. ;10. has evidence of decompensated liver disease or liver cirrhosis.;11.is

pregnant, breastfeeding, or expecting to conceive.;12.is female and is expecting to donate eggs (at any time during the study) or is male and is expecting to donate sperm (at any time during the study).;13.is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ATRIPLA
Generic name:	efavirenz/emtricitabine/tenofovir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MK1439A
Generic name:	doravirine/lamivudine/tenofovir

Ethics review

Approved WMO Date:	12-06-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-003382-17-NL
ClinicalTrials.gov	NCT02403674
CCMO	NL52949.056.15