A Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults

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Primary- To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjectsSecondary- To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks- To...

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

Summary

ID

NL-OMON50555

Source
ToetsingOnline

Brief title
GSK ViiV 204861 / Gemini 1

Condition

- Other condition

Synonym
HIV-1 infection, Human Immunodeficiency Virus-1 Infection

Health condition

HIV-infection

Research involving
Human

Sponsors and support

Primary sponsor: ViiV Healthcare UK Limited
Source(s) of monetary or material Support: ViiV Healthcare

Intervention

Keyword: HIV-1, Treatment Naive

Outcome measures

Primary outcome

Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48

using the FDA Snapshot algorithm [Missing, Switch or Discontinuation = Failure

(MSD=F)] for the intent-to-treat exposed (ITT-E) population

Secondary outcome

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144

using the FDA Snapshot algorithm (MSD=F) for the ITT-E population

- Time to viral suppression (HIV-1 RNA <50 c/mL);

- Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24,

48, 96 and 144;

- Incidence of disease progression (HIVassociated conditions, AIDS and death).

- Incidence of treatment-emergent genotypic and phenotypic resistance to DTG

and 3TC or TDF/FTC in subjects meeting CVW criteria

- Incidence and severity of adverse events (AEs) and laboratory abnormalities;

- Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and 144 weeks

- Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144

- Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144;

- The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;

- Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population

- Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups

- Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study)

Study description

Background summary

Study 204861 is being conducted to compare a simplified two-drug regimen of dolutegravir (DTG) plus lamivudine (3TC) with a standard three-drug first-line regimen in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral therapy (ART)-naïve adult subjects. The study is designed to demonstrate the non-inferior antiviral activity of DTG plus 3TC once daily compared to DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) fixed-dose combination (FDC) once daily at 48 weeks. This study will also characterise the long-term antiviral activity, tolerability and safety of DTG plus 3TC through Week 148. The clinical development programme of DTG plus 3TC aims to develop a FDC tablet of these products.

Study objective

Primary

- To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects

Secondary
- To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks
- To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC over time
- To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria
- To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC over time
- To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC
- To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time
- To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time
- To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC

Study design

This study is a Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. The study will enrol approximately 700 HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to <= 500,000 copies/mL (c/mL). Subjects will be randomised 1:1 to receive a two-drug regimen of DTG plus 3TC once daily (approximately 350 subjects) or DTG plus the FDC tablet of TDF/FTC once daily (approximately 350 subjects) until Week 148. Subjects will be stratified by screening HIV-1 RNA (<= 100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (<= or >200 cells/mm3).

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of1000 to <=100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen*s efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening
HIV-1 RNA of 1000 to <= 500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at <=100,000 c/mL. This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to <=500,000 c/mL for subjects screened on/after 5 November 2016.

Intervention

Eligible subjects will be randomised 1:1 to receive DTG plus 3TC once daily or DTG plus TDF/FTC FDC once daily.

Study burden and risks

Burden:
- ECG: 1x
- Blood sampling: every visit
- Urine sampling: 7x
- Columbia Suicidality Severity Rating Scale: 18x
- Questionnaire (EQ-5D-5L): 7x

See also protocol section 7 (Time and Events Table) of protocol

Dolutegravir (DTG)
Very Common
(could affect 1 in every 10 people or more)
• Headache
• Nausea (feeling sick)
• Diarrhoea or loose stools

Common
(could affect
1 to 10 in every 100 people)
• Rash
• Itching (pruritus)
• Vomiting (being sick)
• Stomach pain and discomfort (upper abdominal pain and abdominal discomfort)
• Difficulty in sleeping (insomnia), abnormal dreams
• Dizziness (or feeling light headed)
• Feelings of deep sadness and unworthiness (depression)
• Anxiety
• Lack of energy (fatigue)
• Flatulence (gas or wind)
• Increase in the level of liver enzymes
• Increase in the level of enzymes produced in the muscles (creatine phosphokinase)

Uncommon
(could affect between 1 in 1,000 and 1 in 100 people)
• Allergic reaction (hypersensitivity)
• Liver toxicity
• An inflammatory condition which may develop as the immune system becomes stronger (immune reconstitution syndrome or *IRIS*)

• Suicidal thoughts and behaviours (mainly in patients who have had depression or mental health problems before)
• Joint pain
• Muscle pain

Lamivudine (3TC)
Common
(could affect
1 to 10 in every 100 people)
• Headache
• Nausea (feeling sick) or vomiting (being sick)
• Stomach pains
• Diarrhoea or loose stools
• Rash
• Hair loss
• Joint and muscle pain
• Lack of energy (fatigue)
• General feeling of being unwell
• High temperature

Uncommon
(could affect between 1 in 1,000 and 1 in 100 people)
• Low white blood cells (blood cells that fight infection)
• Anaemia (low red blood cell count)
• Decrease in the number of platelets (blood cells important for blood clotting)
• Increase in the level of liver enzymes
• Increased fatty acids or sugar in the blood

Rare
(could affect between 1 in 10,000 and 1 in 1,000 people)
• Inflammation of the pancreas (pancreatitis)
• Increase in an enzyme called amylase in the blood
• Serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
• Breakdown of muscles
• Lactic acidosis (see below for more details)

Very Rare
(could affect between 1 in 100,000 and 1 in 10,000 people)
• Failure of the bone marrow to produce new red blood cells (pure red cell aplasia)
• Tingling or numbness of the arms, legs, hands or feet

Tenofovir/emtricitabine (TDF/FTC)
Very Common

(could affect 1 in every 10 people or more)
• Dizziness
• Headache
• Diarrhoea or loose stools
• Nausea (feeling sick) or vomiting (being sick)
• Rash
• Feeling weak
• Decreases in phosphate in the blood
• Increase in the level of enzymes produced in the muscles (creatine phosphokinase)

Common
(could affect
1 to 10 in every 100 people)
• Stomach pain, digestion problems and excessive gas
• Difficulty sleeping; abnormal dreams
• Itching (pruritis); changes in skin colour
• Allergic reactions, including rash, wheezing, shortness of breath, swelling or feeling light-headed
• Low white blood cell count (blood cells that fight infection)
• Increased fatty acids, bile or sugar in the blood
• Changes in liver and pancreas tests

Uncommon
(could affect between 1 in 1,000 and 1 in 100 people)
• Anaemia (low red blood cell count)
• Inflammation of the pancreas (pancreatitis)
• Swelling of the face, lips, tongue or throat
• Muscle pain and weakness
• Decreases in potassium in the blood
• Increased creatinine in the blood
• Changes to amount of protein in the urine

Rare
(could affect between 1 in 10,000 and 1 in 1,000 people)
• Fatty liver
• Inflammation of the liver (hepatitis)
• Passing a lot of urine, feeling thirsty and back pain caused by kidney problems
• Softening of the bones (with bone pain and sometimes resulting in fractures)
• Lactic acidosis (see below for more details)

Contacts

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GB
Scientific
ViiV Healthcare UK Limited

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GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. HIV-1 infected adults >=18 years of age (or older, if required by local regulations), at the time of signing the informed consent.
2. Screening plasma HIV-1 RNA of 1000 c/mL to <=100,000 c/mL. If an independent review of accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen is supportive of the DTG plus 3TC treatment regimen, enrolment will be opened to subjects with Screening plasma HIV-1 RNA of 1000 c/mL to <=500,000 c/mL;
3. Antiretroviral-naïve (defined as <=10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection). Subjects who received HIV postexposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) in the past are allowed as long as the last PEP/PrEP dose was >1 year from HIV diagnosis or there is documented HIV seronegativity between the last prophylactic dose and the date of HIV diagnosis.
4.Male or female.
A female subject is eligible to participate if she is not pregnant as

confirmed by a negative serum human chorionic gonadotrophin (hCG) test at Screening and negative urine test at Baseline), not lactating, and at least one of the following conditions applies:
a.Non-reproductive potential defined as:
•Pre-menopausal females with one of the following:
•Documented tubal ligation
•Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
•Hysterectomy
•Documented Bilateral Oophorectomy
•Postmenopausal defined as 12 months of spontaneous amenorrhea and >=45 years of age [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and oestradiol levels consistent with menopause is confirmatory (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
b.Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 9, Section 12.9.1) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication.
The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.
All subjects participating in the study should also be counselled on safer sexual practices, including the use and benefit/risk of effective barrier methods (e.g. male condom), and on the risk of HIV transmission to an uninfected partner.
5. Subject or the subject*s legal representative capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

Exclusion criteria

1. Women who are breastfeeding or plan to become pregnant or breastfeed during the study;
2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi*s sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm3.

3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification;
4. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);
5. Evidence of HBV infection based on the results of testing at Screening for HBV surface antigen (HBsAg), HBV core antibody (anti-HBc), HBV surface antibody (anti-HBs or HBsAb), and HBV DNA as follows:
• Subjects positive for HBsAg are excluded;
• Subjects negative for anti-HBs but positive for anti-HBc (negative HBsAg status)
and positive for HBV DNA are excluded.
NOTE: Subjects positive for anti-HBc (negative HBsAg status) and positive for anti- HBs (past and/or current evidence) are immune to HBV and are not excluded.
6. Anticipated need for any HCV therapy during the first 48 weeks of the study and for HCV therapy based on interferon or any drugs that have a potential for adverse drug:drug interactions with study treatment throughout the entire study period;
7. Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment). Subjects who are at least 14 days post completed treatment are eligible.
8. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class;
9. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localised malignancies require agreement between the investigator and the Study Medical Monitor for inclusion of the subject.
10. Subjects who in the investigator*s judgment, poses a significant suicidality risk. Recent history of suicidal behaviour and/or suicidal ideation may be considered as evidence of serious suicide risk.
11. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;
12. Treatment with any of the following agents within 28 days of Screening
i. radiation therapy,
ii. cytotoxic chemotherapeutic agents,
iii. any systemic immune suppressant;
13. Treatment with any agent, except recognised ART as allowed above (inclusion criterion 3.), with documented activity against HIV-1 in vitro within 28 days of first dose of study treatment;
14. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study treatment.
15. Subjects enrolled in France (and other countries as required by local regulations or ethics committees/IRBs): the subject has participated in any

study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.
16. Any evidence of pre-existing viral resistance based on the presence of any major resistance-associated mutation [IAS-USA, 2014] in the Screening result or, if known, in any historical resistance test result. NOTE: retests of disqualifying Screening genotypes are not allowed.
17. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening period to verify a result.
18. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject*s participation in the study of an investigational compound.
19. Alanine aminotransferase (ALT) >=5 times the upper limit of normal (ULN) or ALT >=3 x ULN and bilirubin >=1.5 x ULN (with >35% direct bilirubin);
20. Creatinine clearance of <50 mL/min/1.73 m2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

Study design

Design

Study phase:	3
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):	08-12-2016
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epivir
Generic name:	Lamivudine, 3TC
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tivicay
Generic name:	Dolutegravir,DTG
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Truvada
Generic name:	Tenofovir disoproxil fumarate/emtricitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-06-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2020
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	EUCTR2015-004418-95-NL
CCMO	NL57748.078.16

Study results