A Phase IIIb, Randomized, Multicenter, Active-controlled, Parallelgroup, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine administered every two months from a Bictegravir/emtricitabine/tenofovir alfenamide Single Tablet Regimen in HIV-1 Infected Adults who are Virologically Suppressed

Published: 02-09-2020
Last updated: 25-03-2025

Primary:To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every two months compared to a BIK single tablet regimen administered once daily over 12 months in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced...

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

Summary

ID

NL-OMON54886

Source
ToetsingOnline

Brief title
213500 - SOLAR

Condition

- Viral infectious disorders

Synonym
Human Immunodeficiency Virus Type-1; HIV-1 Infection

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BIK single tablet regimen, CAB LA + RPV LA, HIV-1 Infection, supressed HIV-1 infection

Outcome measures

Primary outcome

To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every two

months compared to a BIK single tablet regimen administered once daily:

Proportion of participants with plasma HIV-RNA greater than or equal to 50

copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Month

12 (OLI and BIK)/Month 11 (D2I) (Intent-to-Treat Exposed [ITT-E] population)

Secondary outcome

To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every

2 months compared to a BIK single tablet regimen administered once daily:

Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 6 and

Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I) using the FDA Snapshot

algorithm (Intent-to-Treat Exposed [ITT-E] population)

Proportion of participants with protocol-defined confirmed virologic failure (CVF) through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm at Month 6, and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
Absolute values and changes from Baseline in viral load and CD4+ cell count over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I)

To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure:
Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, BIC, FTC, and TAF through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

To evaluate renal (in urine and blood) and bone (in blood) biomarkers in participants treated with CAB LA + RPV LA compared to BIK: Change from Baseline (Day 1) in renal and bone biomarkers at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

To evaluate Metabolic Syndrome for participants treated with CAB + RPV and BIK:
Change from Baseline in proportions of participants with Metabolic syndrome at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
Change from Baseline in incident metabolic syndrome at Months 6 and 12 (OLI and

BIK)/Month 5 and Month 11 (D2I)

To evaluate insulin resistance in participants treated with CAB LA + RPV LA compared to BIK: Change from Baseline (Day 1) in homeostasis model of assessment-insulin resistance (HOMA-IR) at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

To assess preference for CAB LA + RPV LA administered every 2 months compared to a BIK single tablet regimen administered once daily: Preference for CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen will be assessed using a preference questionnaire at Month 12 (OLI and BIK)/Month 11 (D2I) (or Withdrawal).

To assess patient reported treatment satisfaction, and injection tolerability: Change from baseline (Day 1) in total *treatment satisfaction* score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I), (or Withdrawal)

Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc total score and individual item scores at Month 12 (OLI and BIK)/Month 11 (D2I) (or Withdrawal).

Change from Month 2 in Dimension scores (*Acceptance of ISRs*, *Bother of

ISRs*, *Leg movement*, *Sleep and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time will be assessed using the Perception of injection questionnaire (PIN) at Months 2, 6, and 12 (OLI)/Months 1, 5, 11 (D2I) (or Withdrawal)

Safety:

Incidence and severity of AEs and laboratory abnormalities over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

Proportion of participants who discontinue treatment due to AEs over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

Change from Baseline in laboratory parameters over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

Study description

Background summary

It is estimated that 37.9 million people are currently living with HIV/Acquired Immunodeficiency Syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of 1.7 million new infections and cause 770, 000 deaths per year. Chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

A study by the Antiretroviral Therapy Cohort Collaboration found that of more than 21,000 patients in a European and North American cohort on their first combination antiretroviral therapy (cART) regimen, 51% modified or interrupted

their first cART regimen during a median of 28 months of follow-up with one third of interruptions occurring within the first 6 months of starting therapy. Forty percent of all treatment interruptions were due to the secondary side effects or toxicities of cART, 17% were due to the desire for simplification of the regimen and 14% were due to patient choice. These observations have led to numerous *switch* ART studies, designed to understand the efficacy, safety, and tolerability of switching patients from one regimen to another.

Previous studies have evaluated switches to ritonavir-boosted PI monotherapy in virologically suppressed patients. These studies suggest that simplifying from a three-drug dual class regimen to a single boosted protease inhibitor may be a safe and effective option for the majority of participants studied, who have effectively maintained viral suppression.

CAB LA + RPV LA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.
Three Phase IIb studies (LATTE, LATTE-2 and POLAR) have been conducted with oral CAB and/or IM CAB LA, evaluating an induction/maintenance simplification approach. Three Phase III studies (FLAIR, ATLAS and ATLAS-2M) conducted with CAB LA + RPV LA are ongoing.

Biktarvy (BIK) is a three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen.

Long-acting 2-class therapy consisting of CAB LA + RPV LA as an IM regimen has the benefit of being a NRTI-sparing regimen for long-term treatment of HIV infection which will avoid known NRTI-associated adverse drug reactions and long-term toxicities. Additionally, a 2-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed participants improving the quality of life for people living with HIV.

Study objective

Primary:
To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every two months compared to a BIK single tablet regimen administered once daily over 12

months in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced participants

Secondary:
To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily

To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure

To evaluate renal (in urine and blood) and bone (in blood) biomarkers in participants treated with CAB LA + RPV LA compared to BIK

To evaluate Metabolic Syndrome for participants treated with CAB + RPV and BIK

To evaluate insulin resistance in participants treated with CAB LA + RPV LA compared to BIK

To assess preference for CAB LA + RPV LA administered every 2 months compared to a BIK single tablet regimen administered once daily

To assess patient reported treatment satisfaction, and injection tolerability.

SafetyL
To evaluate the safety and tolerability of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily

Study design

This study is a Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two-drug regimen of CAB LA + RPV LA administered every 2 months compared with maintenance of BIK. Approximately 654 adult HIV-1 infected patients who are on the stable ARV regimen BIK will be randomized 2:1 to either be switched to the CAB LA + RPV LA regimen or continue BIK through 12 months.

Intervention

IM Injections every 2 months (Oral Lead In):
Day 1 - CAB 30 mg + RPV 25 mg oral, administered once daily for 1 month
Month 1 - CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection
Month 2 - CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection
Month 4 and Q2M thereafter - CAB LA 600 mg + RPV LA 900 mg IM, every 2 months until Month 12, each given as 1 X 3 mL IM injection

IM Injections every 2 months (Direct to Injections):
Day 1- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection
Month 1 and Q2M thereafter- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

BIC/FTC/TAF (BIK)
Day 1 - BIC 50 mg + FTC 200 mg + TAF 25 mg oral, administered once daily until Month 12.

Study burden and risks

Side effects associated with CAB (tablets and injections).
CAB when taken together with RPV
In more than 1 in 10 people- headache, pyrexia, injection site reaction
between 1 in 10 people and 1 in 100 people - Rash, diarrhoea or loose stools, nausea, flatulence, Vomiting, Abdominal pain, upper abdominal pain, insomnia, abnormal dreams/nightmares, feeling lightheaded, anxiety, depression, myalgia, fatigue, asthenia, malaise
between 1 in 100 people and 1 in 1,000 people - somnolence (sleepiness or Drowsiness), vasovagal reactions, lightheadedness, light-headedness or fainting, during or following an injection, hepatotoxicity, transaminase increase, weight increase

Hypersensitivity reactions have been reported with other drugs in the same class as CAB (INSTI) with signs and symptoms including general feeling of being sick, skin rash, a high temperature, lack of energy, swelling (sometimes of the face or mouth, causing difficulty in breathing), blisters, mouth ulcers, conjunctivitis, and muscle or joint aches.

Seizures/convulsions have been observed in a small number of HIV-infected study participants receiving CAB (less than 1%). It is unlikely that CAB contributes to seizures, although this cannot be ruled out entirely.

Abnormal liver tests. A small number of participants across CAB research studies developed abnormal liver tests requiring them to stop treatment with CAB. In some of the participants, the abnormal liver tests were explained by other causes (e.g. a new virus infection), while a smaller number of participants (less than 1% of all participants) did not have alternative explanations, suggesting a mild form of liver damage suspected as due to CAB. The liver tests improved after stopping CAB, suggesting that any damage was temporary

RPV (EDURANT)(tablet and Injections):
The RPV tablet is a marketed drug and therefore the side effects are more established than those of CAB, since many more people have received EDURANT.

Skin rash. Most rashes were mild or moderate, happened within the first 4 weeks

of taking RPV, and got better after one week after stopping RPV. However, some types of moderate rash and all types of severe rash, which can be life-threatening, will need participants to stop study medicines (either temporarily or permanently) and come for additional study visits. Some participants with rash may also have other signs and symptoms of allergic reaction.

Abnormal liver tests. Other changes in blood tests have also been observed. Participants with hepatitis B or C or with increases in liver tests showing possible liver damage before starting RPV may have worse liver tests while taking RPV. A few cases of liver problems have also been seen in participants taking RPV who did not already have any liver problems.

Side effects associated with RPV injections:
between 1 in 10 people and 1 in 100 people: Feeling less hungry, sleep disorders, depressed mood, abdominal, discomfort (belly ache), dry mouth
between 1 in 100 people and 1 in 1,000 people: Immune reconstitution syndrome or *IRIS* (an inflammatory condition which may develop as the immune system becomes stronger)

Side effects associated with Bikarvy:
more than 1 in 10 people: Diarrhoea
between 1 in 10 people and 1 in 100 people: headache, nausea, fatigue, joint pain, back pain

Changes in the immune system, kidney problems, including kidney failure, severe liver problems. Too much lactic acid in the subjects blood, which is a serious but rare medical emergency that can lead to death.

Injection site reactions following an injection of CAB LA or RPV LA. The subject may experience local reactions at the spot where he/she received injections (termed *injection site reactions*). Very common side effects could include pain or discomfort, which are usually mild or moderate. The subject may also have redness, swelling, itching, bruising, lumps, infection complications (cellulitis or abscess), and irritation where they get the injection(s). Most reactions go away in a week or less.

The injections will be given in the muscles of the buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering the skin, blood vessel, or a nerve.
The risks of this are not well understood but could make CAB or RPV levels too low or too high. If too low the drug may not work against HIV. If RPV is too high, there could be a change in the heart rate, which very rarely, in severe cases, can be life-threatening and could lead to sudden death; however, to date, no such severe changes in heart rate or sudden deaths have been observed in clinical studies with RPV. In rare cases, high RPV levels immediately after an injection have been associated with feeling lightheaded, numbness or

tingling, difficulty breathing, sweating, feeling nauseous and feeling anxious
Per visit 30-75 ml blood will be drawn. Blood drawl may cause mild pain or bruising.
There is a risk that the virus will become resistant against the (study) drugs against HIV. The risk of the HIV becoming resistant is unknown. It will depend on how well the study drugs work against the virus and how well the subject follows directions on how to take the study drugs

Mental health problems. Some people with chronic health conditions, including HIV, sometimes have feelings of depression or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with CAB and RPV have had suicidal thoughts and actions, particularly those with a prior history of depression or mental health problems.

Contacts

Public
GlaxoSmithKline

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GB
Scientific
GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- 18 years or older
- Women not pregnant, not lactating, or having a Non-reproductive potential or Postmenopausal
- Must be on the uninterrupted current regimen of BIK for at least 6 months prior to
Screening with an undetectable HIV-1 viral load for at least 6 months prior to Screening. Only a single prior INI regimen is allowed if BIK is a second line regimen > 6 months prior to screening.
- Documented evidence of plasma HIV-1 RNA measurements <50 c/mL in the 6 months prior to Screening.
- Plasma HIV-1 RNA <50 c/mL at Screening.

Exclusion criteria

1. Within 6 months prior to Screening, any plasma HIV-1 RNA measurement
50 c/mL
2. Within the 6 to 12-month window prior to Screening, any plasma HIV-1 RNA measurement >200 c/mL, or 2 or more plasma HIV-1 RNA measurements
50 c/mL.
3. History of prior treatment failure to any DHHS recommended ART regimen.
4. History of drug holiday >1 month for any reason prior to Screening visit, except
where all ART was stopped due to tolerability and/or safety concerns
5. Any change to a second line regimen
7. Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed
during the study
8. Any evidence of a current Center for Disease Control and Prevention (CDC) Stage 3 disease, except cutaneous Kaposi*s sarcoma not requiring systemic therapy, and CD4+ counts <200 cells/mm3L are not exclusionary.
9. Participants with moderate to severe hepatic impairment
10. Any pre-existing physical or mental condition (including substance use disorder)
which, in the opinion of the Investigator, may interfere with the participant*s ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant
11. Participants with a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder.
12. Untreated secondary (late latent) or tertiary syphilis infection, defined as a positive RPR and a positive treponemal test without clear documentation of treatment
13. Participants who pose a significant suicide risk.

14. The participant has a tattoo, gluteal implant/enhancements or other dermatological
condition overlying the gluteus region which may interfere with interpretation of
injection site reactions
15. Evidence of Hepatitis B virus (HBV) infection
16. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not
be excluded
17. Unstable liver disease
18. History of liver cirrhosis with or without hepatitis viral co-infection.
19. Ongoing or clinically relevant pancreatitis
20. Clinically significant cardiovascular disease
21. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia;
22. Any condition which, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the participant unable to receive study medication
23. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class.
24. Current or anticipated need for chronic anti-coagulation
25. Corrected QT interval for subjects with bundle branch block.
26. Known or suspected active COVID-19 infection OR has had contact with an individual with known COVID-19, within 14 days of study enrolment.
27. Known or suspected presence of resistance mutations as defined by the IAS-USA
to the individual components of BIK (BIC, FTC, TAF), RPV, and CAB by any historical resistance test result.
28. Any verified Grade 4 laboratory abnormality.
29. Any acute laboratory abnormality at Screening
30. Participant has estimated creatine clearance <30mL/min per 1.73m2
31. Alanine aminotransferase (ALT) >=3 × ULN
32. Exposure to an experimental drug or experimental vaccine within either 30 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 Day 1 of this study
33. Treatment with any of the following agents within 28 days of Screening:
• radiation therapy
• cytotoxic chemotherapeutic agents;
• tuberculosis therapy with the exception of isoniazid
• anti-coagulation agents;
• Immunomodulators that alter immune
34. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening
35. Treatment with any agent, except recognized ART, with

documented activity against HIV-1 within 28 days of study Day 1.
36. Use of medications which are associated with Torsade de Pointes.
37. Participants receiving any prohibited medication

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-01-2021
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Biktarvy
Generic name:	BICTEGRAVIR
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cabotegravir Tablets (CAB)
Generic name:	Cabotegravir Tablets (CAB)
Product type:	Medicine
Brand name:	Edurant
Generic name:	RILPIVIRINE

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rekambys LA
Generic name:	Rilpivirine LA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vocabria LA
Generic name:	Cabotegravir LA
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-09-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-11-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-04-2021
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2020-002623-11-NL
CCMO	NL74638.028.20

Study results

Date completed:	08-03-2022
Results posted:	22-05-2023
Actual enrolment:	9

First publication
03-03-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File