Protocol

Study ID: 207859

Official Title of Study: COMBINE-2: Real-world evidence for effectiveness of TwoDrug Regimen, Antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor

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TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	'COMBINE-2': Real-world evidence for effectiveness of Two Drug Regimen, Antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor
Compound Number:	GSK3365791 (GSK1349572+GSK1329758, Juluca), GSK 3515864 (GSK1349572+GR109714, D3)
Development Phase	IV
Effective Date:	[DD-MM-YYYY]
Subject:	Efficacy of integrase inhibitors plus a reverse transcriptase inhibitor ART.

Author(s):

1. PPD , MD; UNIMORE
2. PPD ; NEAT ID statistician
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4. PPD MD, FRCP; NEAT ID

PASS information

Title	'COMBINE-2': Real-world evidence for effectiveness of Two Drug Regimen, Antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor
Protocol version identifier	v1.0
Date of last version of protocol	
EU PAS register number	Study not yet registered
Active substance	dolutegravir/rilpivirine, dolutegravir/lamivudine
Medicinal product	Invented name: JULUCA
Product reference	JULUCA: H0004427 dolutegravir/lamivudine: H0004909
Procedure number	JULUCA: EMEA/H/C/004427/0000
Marketing authorisation holder(s)	ViiV Healthcare UK Limited
Joint PASS	No
Research question and objectives	Following antiretroviral treatment with the integrase inhibitor dolutegravir plus: a. Reverse transcriptase rilpivirine or; b. Reverse transcriptase lamivudine the study will aim to: 1. Assess the effectiveness of two-drug regimen (2DR – integrase inhibitor plus a reverse transcriptase inhibitor) 2. Collect information on the safety of 2DR in terms of drug related adverse events and serious adverse events, and development of resistance

Country(-ies) of study	Belgium, France, Germany, Italy, Spain, Poland and United Kingdom
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MARKETING AUTHORISATION HOLDER

Marketing authorisation holder(s)	ViiV Healthcare UK Limited 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom

MAH contact person	Dr. PPD GlaxoSmithKline R&D Limited Stockley Park West Uxbridge Middlesex UB11 1BT United Kingdom

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1. LIST OF ABBREVIATIONS

2DR	Two-drug regimen
ACTG	AIDS Clinical Trial Group
AE	Adverse Event
AR	Adverse Reaction
ART	Antiretroviral Therapy
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DTG	Dolutegravir
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN Number	International Standard Randomised Controlled Trials
3TC	Lamivudine
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PASS	Post-authorization Safety Study
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
RPV	Rilpivirine

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

Trademark Information

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SAS
Stata
SPSS

2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

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Sponsor Legal Registered Address:

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Date

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Nassrin Payvandi
VP, Head of Safety and Pharmacovigilance

PPD

Date

CHIEF INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I agree to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name: Dr. Cristina Mussini

PPD

6th June 2018

Investigator Signature | Date

3. ABSTRACT

The efficacy of two-drug regimen (2DR) therapy with an integrase inhibitor plus a reverse transcriptase inhibitor is being assessed in various pilot studies and clinical trials. In the PADDLE study, high rates of HIV RNA suppression were demonstrated after first-line treatment with Dolutegravir (DTG) plus Lamivudine (3TC)[1]. Other studies have shown high rates of HIV RNA suppression after patients with HIV RNA suppression at baseline on triple therapy were switched to 2DR with DTG plus 3TC. Phase III, SWORD 1 and SWORD 2 clinical trials for investigational 2DR of DTG and RPV for HIV treatment, achieved non-inferior viral suppression at 48 weeks compared with a three- or four-drug regimen[2].

However, the pilot studies conducted to date and the Phase 3 programme all have strict inclusion/exclusion criteria.

Thus, gathering real world evidence with less restrictive inclusion criteria to evaluate effectiveness of the 2DR with an integrase inhibitor such as DTG plus a reverse transcriptase inhibitor such as 3TC or RPV would further demonstrate the value of such regimen.

This multi-site observational study will assess the effectiveness of 2DR in approximately 500 patients either as:

- a first-line treatment for naïve patients,
- a switching option for those with HIV RNA suppression on current treatment (stable switch),
- or a second-line treatment for those with virological failure (VF) on prior treatment.

The data collected for this study does not require any changes to the routine standard of care that patients receive. The study will aim to assess effectiveness of this regime with HIV RNA suppression below 50 copies/mL after 24 weeks of treatment, 48 weeks of treatment and a long term follow-up analysis at 96 weeks.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason

5. MILESTONES

Milestone	Planned date
Start of data collection	Dec-2018
End of data collection	Dec-2021
Annual study progress reports	Yearly, within 30 days of the anniversary date of EC approvals.
Final report of study results	Nov-2022 or within 12 months after end of study

6. RATIONAL AND BACKGROUND

The efficacy of two-drug regimen (2DR) therapy with an integrase inhibitor plus a reverse transcriptase inhibitor is being assessed in pilot studies and clinical trials. Dolutegravir (DTG) is a well tolerated 2nd generation integrase strand transfer inhibitor (INSTI); rilpivirine (RPV) is a well tolerated NNRTI and lamivudine (3TC) is an nucleoside reverse transcriptase inhibitors (NRTIs). In the PADDLE study, high rates of HIV RNA suppression were demonstrated after first-line treatment with DTG plus 3TC. Other studies have shown high rates of HIV RNA suppression after patients with HIV RNA suppression at baseline on triple therapy were switched to 2DR with DTG plus 3TC. Other pilot studies are in progress: DOLBI in Spain, LAMIDOL in France and an ACTG-sponsored trial in the USA. In addition, the Phase 3 GEMINI 1 and 2 trials are in progress for DTG plus 3TC. These registrational, double-blinded trials randomise patients to receive first-line treatment with either triple therapy or DTG plus 3TC, with a combined sample size of over 1400 patients.

SWORD 1 and SWORD 2 studies, the phase III clinical trials for investigational 2DR of DTG and RPV for HIV treatment, achieved non-inferior viral suppression at 48 weeks compared with a three- or four-drug regimen. This programme comprised of two studies with over 1000 patients who previously achieved viral suppression on a three- or four-drug ART. These patients were randomised to either stay on their three- or four-drug regimen or switch to a DTG plus RPV regimen[2].

The pilot studies conducted to date and the Phase 3 programme all have strict inclusion/exclusion criteria. For example the PADDLE study excluded people who had screening HIV RNA levels above 100,000 copies/mL (although 3 patients had VL higher than this at baseline).

Thus, gathering real world evidence in this multi-site observational study with less restrictive inclusion criteria to evaluate effectiveness of the 2DR would further demonstrate the value of such regimen.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The study will aim to assess the effectiveness of 2DR, following an Antiretroviral treatment with integrase inhibitors DTG plus a reverse transcriptase inhibitor RPV or 3TC; in patients either as a first-line treatment in naïve patients, a switching option for those with HIV RNA suppression on current treatment (stable switch), or a second-line treatment for those with VF on prior treatment.

7.1. Primary Objective:

a) To assess the effectiveness of a 2DR (integrase inhibitor plus a reverse transcriptase inhibitor).

7.2. Secondary Objective:

a) To collect information on the safety of a 2DR in terms of drug related AEs, SAEs and development of resistance.

8. RESEARCH METHODS

8.1. Study Design

This is a multi-site observational study across Europe in patients who have started and/or who plan to initiate 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor will be eligible for this study. We anticipate that the majority of these patients will be taking either DTG plus RPV, or DTG plus 3TC.

The study does not require any changes to the routine standard of care that patients receive, and decisions on ARV treatment are made by the healthcare providers taking into account the treatment history, patient characteristics and local guideline or recommendations. Data will be collected every 6 months from participating sites for a period of 96 weeks for each potential patient.

8.2. Study Population and Setting

8.2.1. Study Setting

Potential NEAT-ID investigational sites across Europe will be contacted for feasibility and if they already have patients taking dual combinations of an integrase inhibitor plus a reverse transcriptase inhibitor. Sites with at least 5 patients already taking this treatment (outside clinical trials) since January 2014 or who plan to initiate at least 5 patients in near future will be selected to participate in this study.

NEAT ID Network team will perform site visits to assess protocol issues, consent, data quality and Study Management quality performance.

8.2.2. Inclusion Criteria

The study population will consist of HIV positive male or female aged 18 years or over and who have started 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor from 2014 onwards as:

a) a first-line treatment among naïve patients, or
b) a switching option for those with HIV RNA suppression on current treatment (stable switches), or
c) a second-line treatment for those with virological failure (VF) on prior treatment.

8.2.3. Patient Identification and Consent

The aim is to include at least 500 patients across Europe Once all relevant approvals are in place for the protocol, selected investigational sites will be contacted and asked to identify potential patients on 2DR either retrospectively and/or potential prospective pateints. Consent procedures will be undertaken as required by country specific regulations and local procedures for the collection of retrospective and/or prospective data. These patients will not need to attend any additional visits or undergo any procedures above their routine standard of care.

8.3. Variables

8.3.1. Exposure definitions

Any exposure to integrase inhibitors such as DTG and reverse transcriptase inhibitors such as 3TC or RPV is of interest. Exposure starts the first day ART of an integrase inhibitor plus a reverse transcriptase inhibitor are known to have taken. Person time exposed is defined as the number of days that the subject is known to have been exposed to this dual combination regimen.

8.3.2. Outcome Definitions

8.3.2.1. Primary Outcomes

a) For treatment-naïve patients: the proportion of patients with HIV-RNA levels <50 copies/mL at 24, 48, and 96 weeks, estimated using a Kaplan-Meier Method. Participants with virologic rebound or virologic non-response will be considered as failure.
   Virologic rebound will be defined as two consecutive measurements of >50 copies/mL after suppression (one <50 copies/mL)
   Virologic Non-response will be defined as two consecutive measurements of >50 copies/mL after at least 24 weeks of treatment

b) For stable switch patients: the proportion of patients who lose virologic control (2 consecutive HIV RNA levels >50 copies/mL or HIV RNA >50c/mL followed by

study treatment discontinuation or missing value) within the first 24, 48 and 96 weeks after switching to a 2-DR, estimated using a Kaplan-Meier Method.

c) For treatment-experienced patients with VF on current treatment: the proportion of patients with HIV-RNA levels <50 copies/mL at 24, 48, and 96 weeks, estimated using a Kaplan-Meier Method. Participants with virologic rebound or virologic non-response will be considered as failure.
Virologic rebound will be defined as two consecutive measurements of >50 copies/mL after suppression (one <50 copies/mL)
Virologic Non-response will be defined as two consecutive measurements of >50 copies/mL after at least 24 weeks of treatment

Treatment effectiveness will also be assessed by using the following definition for virologic rebound and virologic non-response:

For naïve and switch with VF populations

a) Virologic Rebound: two consecutive measurements of ≥200 copies/mL after suppression (one <50)
b) Virologic Non-response: two consecutive measurements of ≥200 copies/mL after at least 24 weeks of treatment

For stable switch populaion

c) Virologic Rebound: 2 consecutive HIV RNA levels >200 copies/mL or HIV RNA >200c/mL followed by study treatment discontinuation or missing value

8.3.2.2. Secondary Outcomes

In each population (naïve, stable switch, and treatment-experienced with VF):

a) Proportion of patients with HIV RNA >200 copies/mL after 24, 48 and 96 weeks of treatment. (to analyse in real world and quantify the blips).
b) Proportion of patients with low level viremia (VL >50 and <200 copies/mL) at each time point for analysis.
c) Time to virologic suppression in the naïve and the switch with VF populations (viral load < 50 copies/mL at the end of 6months/12months/18 months or as pre-specified. This allows for blips during the follow up period).
d) Time to VF in the stable switch population
e) Resistance profile in case of virological failure
f) Proportion of patients with:
    1. Stable switch while virologically suppressed
    2. Switch after Failure
    3. Switching for tolerability, toxicity and other reasons
g) Frequency of drug related AEs and SAEs
h) Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0.

i) Factors associated with plasma HIV-RNA > 50 copies/mL after 96 weeks if number of failures allows analysis

8.3.3. Confounders and Effect Modifier

We will examine factors associated with VF.

8.4. Data Sources

Data will be collected from all participating European sites. Following all relevant approvals, selected sites will be contacted and asked to identify patients currently on 2DR and collect data either retrospectively and/or identify prospective patients to start this treatment. Pseudo anonymised data will be collected by electronic transfer of datasets from each site.

The following data will be collected if available for each participant and updated information included in the 6 monthly data transfer / collection:

1. Baseline characteristics – age, gender, ethnicity, CD4 and CD8 count at time of first starting 2DR treatment, CD4 nadir, CDC disease stage.
2. Duration of undetectability plasma HIV RNA levels at start of 2DR treatment, where available
3. HIV RNA data – all available HIV RNA results since first starting antiretroviral treatment, with dates. Data on last viral load above 50 copies/mL.
4. Immunological data: all available CD4 and CD8 results since first starting 2DR treatment.
5. Antiretroviral treatment history – all antiretrovirals taken since first-line treatment (if not naïve) started, with dates. Reasons for stopping or switching each treatment and related toxicity data.
6. Resistance tests – results of all HIV resistance tests performed before and during antiretroviral treatment.
7. Co-morbidities and all co-medications
8. All available drug related AEs and SAEs since starting DTG+RPV or DTG+3TC.

8.5. Study Size

The expected sample size for this study is 500 patients.

a) In ARV naïve population, the expected success rate of a standard 3-drug regimen can be estimated at 90% at week 48 (based on SNGLE, SPRING-2 and FlAMINGO trials results) with a non-inferiority margin of 10% (see FDA guidelines). Therefore the 2-DR will be considered acceptable if the percentage of patients in success (HIV RNA <50 copies/mL) at week 48 is significantly above 80%. Assuming a 90% response rate, by including 90 individuals, we will have a 95 % probability to discard a combination for which efficacy is smaller than 80 % and we will select with a power of >80 % the strategy for which the efficacy is above or equal to 90%.

b) In patients switching with HIV RNA suppression (Stable switch population), the expected VF rate of a standard 3-drug regimen can be estimated at 4% at week 48 (based on NEAT22/SSAT60 trial result, IAS2017) with a non-inferiority margin of 4%. Therefore, the 2-DR will be considered acceptable if the percentage of patients in VF at week 48 is significantly lower than 8%. Assuming a 4% VF , by including 320 individuals, we will have a 95% probability to discard a combination for which the rate of failure is greater than 8% and we will select with a power of >90% the strategy for which the rate of failure is less to 8%.

c) In a population of patients with a second line treatment due to VF on prior treatment, the expected success rate of a standard 3-drug regimen can be estimated at 90% at week 48 (based on the 24-week result (82%) of DTG-containing regimen in the DAWNING trial) with a non-inferiority margin of 10% (see FDA guidelines). Therefore the 2-DR will be considered acceptable if the percentage of patients in success (FDA snapshot method) at week 48 is significantly above 80%. Assuming a 90% response rate, by including 90 individuals, we will have a 95 % probability to discard a combination for which efficacy is smaller than 80 % and we will select with a power of >80 % the strategy for which the efficacy is above or equal to 90%.

For the above power calculations a total of at least 90 naïve, 320 stable switch patients and 90 second line treatment due to VF patients should be included. However, if the number of patients in naïve and VF cohorts are insufficient to fulfill the power calculations, these cohort data will be used for descriptive purposes only.

8.6. Data Management

8.6.1. Data Collection

8.6.1.1. Source Data

Source data are contained in source documents (original records or certified copies) maintained at site. No additional data will be collected for this study, data will be collected as part of routine standard of care data only.

8.6.1.2. Source Documents

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) will be maintained at site in accordance with usual standard of care

The subject's number and date of entry into the study, along with a study identifier, should be recorded in the subject's study records.

8.6.1.3. Data Collection Methods

In order to maintain confidentiality, the subject will be identified only by subject number.

Subject data will be collected via extraction from electronic source data by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the Principal Investigator (PI). A delegation of responsibility log will be updated accordingly.

Sites will provide / upload data every 6 months to the data management team who will store the data on a secure network drive with access to authorised personnel of the data management team only, maintained on a log of authorised personnel by the sponsor representative.

8.6.2. Data Handling Conventions

Data will be handled in accordance with data handling guidelines provided to sites.

The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required.

Identified only by subject number, the data are pseudo-anonymised at all times and are transferred securely. All transfers are fully documented.

8.6.3. Resourcing Needs

The study will be overseen and managed by NEAT-ID. NEAT-ID will assign a Project Manager to the study who will oversee the day to day activities of the trial and manage the mutidiscpliary project team.

ViiV as sponsor will retain all repsonsibilities in relation to regulatory reporting.

8.6.4. Timings of Assessment During Follow-up

Available data will be collected from enrolled participants every 6 months and transferred to the data coordinating centre.. Participant involvement in this study will end after week 96 data collection.

8.7. Data Analysis

The statistical analysis plan will be produced during the early stages of the study, after protocol finalization. This statistical analysis plan will describe the primary and secondary analysis and the format of the final tables, figures and listings to be generated. Data will be analysed using SAS, SPSS or STATA.

8.7.1. Essential Analysis

We will separately evaluate the efficacy of the 2DR according to prior treatment status; first-line treatment for naïve patients, stable switching with HIV RNA suppression, or switching after VF. The primary effectiveness endpoint will be analysed with an

Intention-to-treat (ITT approach). The 95% two-sided confidence interval (CI) of the observed proportion of patients reaching the effectiveness endpoint will be calculated.

In the treatment naïve and treatment experienced with VF individuals, the primary endpoint is the proportion of patients with HIV RNA suppression below 50 copies/mL after 24, 48 and 96 weeks of treatment, estimated using Kaplan-Meier method standard. 2DR will be considered as an acceptable strategy in these populations if the lower bound of the 95% CI is greater than 80%.

In the stable switch population, the primary endpoint is the proportion of patients with VF at weeks 24, 48 and 96 (defined as 2 consecutive plasma HIV RNA >50 copies/mL, or Plasma HIV RNA>50 c/mL followed by study treatment discontinuation or missing value). The 95% CI of the observed proportion of patients reaching the efficacy endpoint will be calculated with the Kaplan-Meier method, censoring at week 48 or last follow-up date if missing HIV RNA viral load values at week 48. 2DR will be considered as an acceptable strategy in this population if the upper bound of the 95% CI is lower than 8%.

Grade 3 and 4 adverse events, ART related adverse events (all grades), treatment-modifying adverse events (all grades); AIDS defining event, death, study treatments discontinuation, as well as serious adverse events (SAE) will be described, between 0-24, 24-48, and 48-96 weeks.

Changes from baseline in continuous endpoints in each population (naïve, stable switch, treatment-experienced with VF) between baseline and week 24, 48 and 96 will be compared by using Wilcoxon's paired test with the ITT population (last observation carried forward (LOCF) or other imputation method to be defined in the statistical analysis plan). We will use percentage and 95 % two-sided confidence interval to describe the qualitative endpoints, their change over time will be tested with a McNemar test with a 5 % Type I error. Linear mixed models will also be used to estimate and compare the evolution of CD4, CD8 count and CD4/CD8 ratio over time.

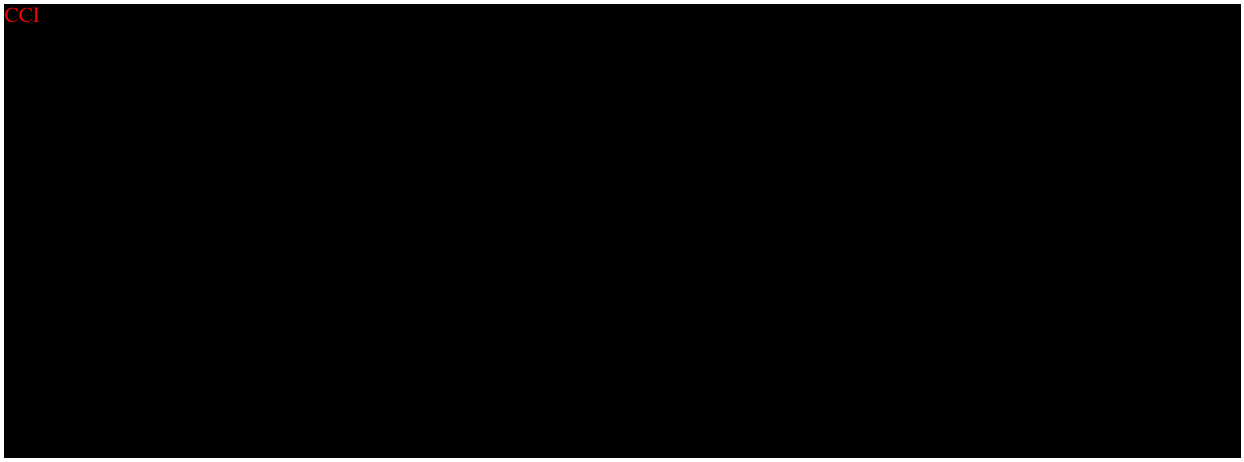
The number of included patients and the flowchart of the trial will be presented. The baseline patients' eligibility and characteristics of the ITT population will be described. Quantitative variables will be described by their means, standard deviations, medians, Interquartile range (IQR), minimums and maximums. For qualitative variables, figures and percentages per class will be presented or method will be given. All protocol deviations and their reasons will be described.

An interim analysis will be conducted after 24 weeks of treatment, the primary endpoint analysis will be conducted after 48 weeks of treatment and a long-term follow up analysis will be conducted after 96 weeks of treatment.

Historical data from studies like STRIIVING, WAVES, DAWNING, FLAMINGO, SINGLE, SPRING I and II shall be used as a comparator for analysis.

CCI

[redacted]



8.8. Quality Control and Quality Assurance

Electronic data sets will provide an unmonitored subset of existing source data that will be subject to data validation. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process.Data will be analysed by a Statistician skilled in population bases analysis using SAS, SPSS or STATA.

NEAT-ID may decide to include this study in the annual audit schedule. The audit conduct and reporting will be preformed by the independent QA personnel and in accordance with the GCP and the applicable NEAT-ID Standard Operating Procedures.

8.9. Limitations of the Research Methods

Limitations of this study are common to non-randomized non-interventional study. Selection bias may be present as the sites may elect to enroll participants that may have a better or worse health status compared to the general HIV positive treated population. Channeling bias may also be present.

8.9.1. Study Closure/Uninterpretability of Results

Both the sponsor and the NEAT-ID collaboration reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies, IRBs, and IECs. In terminating the study, sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects'interests.

Following completion of the study, any study documentation will be retained by the Investigator in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval

Before the start of data collection, this protocol and any accompanying material to be provided to the patients (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted to Ethics Committee (EC) in the relevant countries. The investigator will not begin any study activities until approval from the EC has been documented and provided as a letter to the investigator.

Any subsequent amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study which will be disseminated to the investigator and sites (NOTE: amendments may also need to be reviewed and accepted by the regulatory agencies and/or local EC departments before they can be implemented in practice at sites)

An annual progress report will be submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. NEAT ID will produce the annual reports as required.

NEAT ID team will notify the EC of the end of the study. If the study is ended prematurely, NEAT ID will notify the EC, including the reasons for the premature termination.

9.2. Subject Confidentiality

All investigators and study site staff will comply with the requirements of the current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles.

Personal information is to be collected, kept secure, and maintained in line with the following requirements:

- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders/storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If during the study, a drug related adverse event (serious or non serious) is identified as being related to any ViiV Healthcare product (including products not covered in the specific study objective), this will be reported to the GSK Central Safety Department by email of fax. All drug related SAEs and pregnancy exposures will be reported within 24

hours (3 calendar days in case of a weekend) of first becoming aware of the event. Non-serious drug related AEs related to any ViiV/GSK products will be reported within 5 calendar days (7 calendar days in case of a weekend) of first becoming aware of the event.

All drug related serious and non-serious AEs, pregnancy exposures or incidents associated with any ViiV Healthcare product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP). This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier/Vendor staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Investigator and site staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Safety-specific roles
- ADRs, SAEs, pregnancy outcomes, and incident collection and reporting processes
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

10.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE does not include the following: • Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE. • Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

	• Any medical condition or clinically significant laboratory abnormality with an onset date before baseline are considered to be preexisting conditions and should be documented as medical history.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between the drug and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the drug qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation unless hospitalization is for: o Routine treatment or monitoring of the studies indication, not associated with any deterioration in condition. o Elective or pre-planned treatment for pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study drug. o Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of SAE given above and not resulting in hospital admission. o Social reasons and respite care in the absence of any deterioration in the patient's general condition. • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect • Is medically significant, i.e. defines as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. • All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT 3xULN and bilirubin 2xULN (>35% direct*) *Note: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2xULN, then the event is still reported as an SAE. INR elevations of >1.5 suggest severe liver injury.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

10.2. Assessment of Adverse Events and Serious Adverse Events (SAE)

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and for final review and confirmation of accuracy of event information and assessments.

10.3. Assessment of Causality for Study Drugs

The relationship to study drug of each adverse event will be assessed taking into consideration the following:

- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator/subinvestigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The approved Product Information (SmPC) for marketed each marketed product should be used in consideration of this assessment

A causality assessment should be provided on all AE/SAE forms reported to ViiV/GSK.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience includes healthcare providers, patient groups, regulatory and health authorities.

Interim and final study results will be presented at conferences such as but not limited to CROI and/or IAS, and followed by a publication in relevant peer-reviewed medical scientific journal and relevant newsletters.

11.2. Study Reporting and Publications

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the EC. ViiV Healthcare will submit the study report to the regulatory agencies.

A publication of the results will be prepared at week 24 data and 48 data outcome from first 200 patients and week 48 data outcome from at least 500 patients.

12. REFERENCES

1. **Cahn P, Rolon MJ, *et al.*** Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *J Int AIDS Soc*. (2017) May 9;20(1):21678.
2. **Josep L, Chien-Ching H, *et al.*** Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* (2018), ISSN: 1474-547X, Vol: 391, Issue: 10123, Page: 839-849.

ANNEX 1: Data Assessment Table

Data collected	Timepoints	
	Baseline (day0)	Treatment (day1-96weeks)
Age	X	
Gender	X	
Ethnicity	X	
Medical History: • Nadir CD4 • HIV resistance tests • ARV history	X	
CD4 count[1]	X	X
CD8 count[1]	X	X
HIV RNA data	X[2]	X
CDC disease stage	X (Calculated assessment)	
Duration of undetectable plasma HIV RNA results	X	
ARV treatment history		X[3]
HIV Resistance tests	X[7]	X[4]
Co-morbidities		X[5]
Co-medications		X[5]
Side effects/toxicity		X[6]

Footnotes:

1. Baseline before starting 2DR (DTG+RPV or DTG+3TC), and all available results after starting 2DR
2. All data since first starting ARV with dates.
3. Antiretroviral name and date of treatment, reasons for stopping, switching each treatment and related toxicity
4. During the 2DR treatment , date of resistance test and test results
5. Within 6-12 months of 2DR
6. Only DTG+RPV and DTG+3TC related side effects and toxicity.
7. Resistance tests will only be done if naive detectable or switch or VF.

ANNEX 2: AIDS Clinical Trial Group (ACTG) Grading Scale

DAIDS AE Grading Table Corrected Version 2.1-July 2017

Attached as a separate document, and available online at:

https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf?sfvrsn=6