AN OPEN-LABEL, MULTI-CENTRE, RANDOMISED, SWITCH STUDY TO EVALUATE THE VIROLOGICAL EFFICACY OVER 96 WEEKS OF 2-DRUG THERAPY WITH DTG/RPV FDC IN ANTIRETROVIRAL TREATMENT-EXPERIENCED HIV-1 INFECTED SUBJECTS VIROLOGICALLY SUPPRESSED WITH NNRTIS RESISTANCE MUTATION K103N.

-WISARD-

Version 5.0 dated 30Oct2020

Sponsor number: SSCR105/NEAT33

EudraCT: 2017-004040-38

Sponsor: NEAT ID

Private & Confidential

GCP Compliance Statement:
This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki and all applicable regulatory requirements

SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the trial Sponsor:

e-signature provided by: FULL NAME, TITLE/ROLE

Chief Investigator:

e-signature provided by: FULL NAME, TITLE/ROLE

STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Statistician or Study Analyst agrees to conduct the trial in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Statistician or Study Analyst:

e-signature provided by: FULL NAME, TITLE/ROLE

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with ICH-GCP and the applicable regulatory requirements and with the approved protocol.

I agree to comply with the procedures for data recording/reporting.

I agree to permit monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to ICH-GCP.

Principal Investigator:

e-signature provided by: FULL NAME, TITLE/ROLE

TABLE OF CONTENTS

SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE 2

STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE 3

PRINCIPAL INVESTIGATOR SIGNATURE PAGE 4

TABLE OF CONTENTS 5

KEY TRIAL CONTACTS 8

STUDY SYNOPSIS 9

LIST OF ABBREVIATIONS 12

1. BACKGROUND & RATIONALE 16

1.1. ASSESSMENT AND MANAGEMENT OF RISK 16

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS 23

2.1 PRIMARY OBJECTIVE 23
2.2 SECONDARY OBJECTIVES 23
2.3 OUTCOME MEASURES/ENDPOINTS 23
2.3.1 PRIMARY ENDPOINT/OUTCOME 23
2.3.2 SECONDARY ENDPOINTS/OUTCOMES 23
2.4 EXPLORATORY ENDPOINTS/OUTCOMES 24

3 TRIAL DESIGN 25

3.1 STUDY SCHEMA 26

4 STUDY SETTING 26

5 ELIGIBILITY CRITERIA 27

5.1 INCLUSION CRITERIA 27
5.2 EXCLUSION CRITERIA 28

6 TRIAL PROCEDURES 32

6.1 RECRUITMENT 32
6.2 STUDY REGISTRATION 32
6.3 PATIENT IDENTIFICATION 32
6.4 SCREENING 33
6.5 CONSENT 34
6.6 RANDOMISATION 35
6.6.1 THE RANDOMISATION SCHEME 35
6.6.2 METHOD OF IMPLEMENTING THE ALLOCATION SEQUENCE 35
6.6.3 BLINDING 35
6.6.4 UNBLINDING 35
6.7 BASELINE DATA 35
6.8 STUDY ON TREATMENT VISITS 36
6.9 FOLLOW-UP ASSESSMENTS 38

6.10 EARLY TERMINATION VISIT 38
6.11 QUALITATIVE ASSESSMENTS – NESTED STUDIES 39
6.12 WITHDRAWAL CRITERIA 39
6.13 LIVER CHEMISTRY STOPPING AND FOLLOW UP CRITERIA 42
6.14 SUICIDAL RISK MONITORING 45
6.15 DECLINE IN RENAL FUNCTION 46
6.16 PROTEINURIA 47
6.17 CREATINE PHOSPHOKINASE (CPK) ELEVATION 47
6.18 STORAGE AND ANALYSIS OF SAMPLES 48
6.19 VIROLOGICAL FAILURE 48
6.20 END OF TRIAL 48

7 TRIAL MEDICATION 49

7.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S) 49
7.2 REFERENCE SAFETY INFORMATION 49
7.3 DRUG STORAGE AND SUPPLY 50
7.4 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT 50
7.5 DOSAGE SCHEDULES 51
7.6 DOSAGE MODIFICATIONS 51
7.7 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES 51
7.8 CONCOMITANT MEDICATION 52
7.9 PRIOR CONCOMITANT THERAPY 52
7.10 TRIAL RESTRICTIONS 52
7.11 ASSESSMENT OF COMPLIANCE 53
7.12 PROVISION OF TREATMENT AFTER THE END OF THE TRIAL 53

8 PHARMACOVIGILANCE 53

8.1 DEFINITIONS 53
8.2 OPERATIONAL DEFINITIONS FOR (S) AES 54
8.2.1 ASSESSMENT OF INTENSITY 55
8.2.2 ASSESSMENT OF CAUSALITY 56
8.2.3 COLLECTION AND FOLLOW UP OF ADVERSE EVENTS 56
8.2.4 SERIOUS ADVERSE EVENTS (SAE) & REPORTABLE EVENTS 57
8.3 RECORDING AND REPORTING OF SAES AND SUSARS 58
8.3.1 REPORTING REQUIREMENTS 58
8.4 RESPONSIBILITIES 61
8.5 REPORTING URGENT SAFETY MEASURES 63
8.6 DEVELOPMENT SAFETY UPDATE REPORTS (DSUR) 63

9 STATISTICS AND DATA ANALYSIS 63

9.1 SAMPLE SIZE 63
9.2 STATISTICAL ANALYSIS PLAN 64
9.2.1 Summary of baseline data and flow of patients 65
9.2.2 Primary outcome analysis 65
9.2.3 Secondary outcome analysis 66
9.3 SUBGROUP ANALYSES 66
9.4 ADJUSTED ANALYSIS 66

9.5 INTERIM ANALYSIS 66
9.6 DSMB 67
9.7 SUBJECT POPULATION 67
9.8 PROCEDURE(S) TO ACCOUNT FOR MISSING OR SPURIOUS DATA 68
9.9 OTHER STATISTICAL CONSIDERATIONS 68
9.10 ECONOMIC EVALUATION 68

10 DATA HANDLING 68

10.1 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION 68
10.1.1 SOURCE DATA 68
10.1.2 SOURCE DOCUMENTS 68
10.1.3 CASE REPORT FORMS 69
10.2 DATA HANDLING AND RECORD KEEPING 70
10.3 ARCHIVING 70

11 MONITORING, AUDIT & INSPECTION 71

12 ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/ GROUPS & INDIVIDUALS 72

13 ETHICAL AND REGULATORY CONSIDERATIONS 73

13.1 ETHICS COMMITTEE (EC) REVIEW & REPORTS 73
13.2 PEER REVIEW 73
13.3 REGULATORY COMPLIANCE 74
13.4 PROTOCOL COMPLIANCE 74
13.5 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL 74
13.6 DATA PROTECTION AND PATIENT CONFIDENTIALITY 75
13.7 FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT 75
13.8 INDEMNITY 75
13.9 AMENDMENTS 75
13.10 POST TRIAL CARE 76
13.11 ACCESS TO THE FINAL TRIAL DATASET 76

14 DISSEMINIATION POLICY 76

14.1 DISSEMINATION POLICY 76

15 APPENDICES 77

APPENDIX 1: ASSESSMENT TABLE 78
APPENDIX 2: AIDS CLINICAL TRIAL GROUP (ACTG) GRADING SCALE, DAIDS GRADING SCALE 83
APPENDIX 3: HIGHLY EFFECTIVE METHODS FOR AVOIDING PREGNANCY IN FEMALES OF CHILD BEARING POTENTIAL 84
APPENDIX 4: THE CHILD-PUGH CLASSIFICATION SYSTEM 85
APPENDIX 5: DATA PROCESSING AGREEMENT 86
APPENDIX 6: AMENDMENT HISTORY 89

KEY TRIAL CONTACTS

Chief Investigator	[redacted]
Sponsor	[redacted]
Project Management	[redacted]
Data Management	[redacted]
Statistics	[redacted]
Peripheral Blood Monoclonal Cell (PBMC) Central Laboratory	[redacted]
PK Central Laboratory	[redacted]

STUDY SYNOPSIS

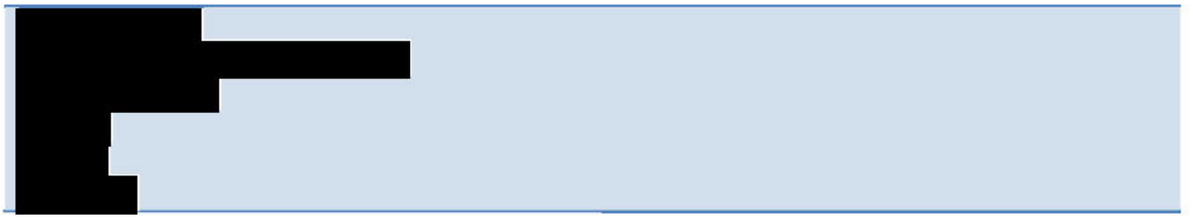
Full study Title	An open-label, multi-centre, randomised, switch study to evaluate the virological efficacy over 96 weeks of 2-drug therapy with DTG/RPV FDC in antiretroviral treatment-experienced HIV-1 infected subjects virologically suppressed with NNRTIs resistance mutation K103N.
Short title/Acronym	WISARD: acronym of **SWI**tch Study mut**A**tion **R**ilpivirine **D**olutegravir.
Clinical Phase	3b
Trial Design	Open-label, 2 arm, phase 3b, multi-centre switch study
Name of Investigational Product	Dolutegravir & Rilpivirine 2 drug fixed dose combined therapy. "Juluca" is the brand name and will hereinafter be referred to as combined dolutegravir (DTG) and rilpivirine (RPV). Investigational product may be provided as commercial "Juluca" or unbranded supply of DTG + RPV. Boosted protease inhibitors or other ARV regimen (including Anatomical Therapeutic Chemical Classification System codes: JO5AB, JO5AE, JO5AF, JO5AG, JO5AR, JO5AX)
Trial Participants population	≥ 18years, male & female
Planned Sample Size	Up to 150 evaluable subjects.
Eligibility Criteria	HIV-1 infected adults aged 18 years or over, virologically suppressed with NNRTIs resistance mutation K103N. (Subjects who at any time have had the mutations 100I, 101E/P, 106A/M, 138K/G/Q, 181C/I/V, 188L, 190A/S/E/Q, 230L mutations are to be excluded. Other NNRTI region variants can be included).
Treatment duration	96 weeks
Follow up duration	30 days
Formulation, Dose, Route of Administration	Experimental arm (Baseline visit switch group): One combined Dolutegravir 50mg /Rilpivirine 25mg FDC tablet taken orally once daily for 96 weeks. Control arm (deferred week 48 switch group): patients will continue their current boosted PI regimen (or other antiretroviral combination) for 48 weeks. Patients will then be switched to one combined Dolutegravir/Rilpivirine FDC tablet taken orally once daily for 48 weeks.
Indication	HIV-1 infected patients with a history of virological failure to NNRTIs and having the K103N mutation.
Methodology	Eligible consented patients will be randomised 2:1 to switch to the experimental arm or continue on their current therapy and switch at week 48(control arm). Efficacy will be assessed by maintenance of virological success.
Number of sites	36 sites in 7 countries (United Kingdom, France, Belgium, Germany, Spain, Italy & Ireland)

Objectives **(See also section 2.4 for exploratory objectives)**	**Primary** 1. To compare viral load outcomes on DTG/RPV FDC regimen (experimental arm) to continued ART regimen (control arm) at 48 weeks as measured by HIV-1 RNA below or confirmed above 50 copies/Ml.	**Secondary** 1. To investigate whether switching patients to DTG/RPV FDC is associated with improvement of lipid profile, patient satisfaction, quality of life and potential for drug-drug interactions. Investigated over 96 weeks with evaluation at week 24, 48 & 96. 2. To evaluate DTG & RPV trough concentrations 3. Changes in cell associated virus (using PBMC analysis)
Outcome Measures	**Primary** a. Virological suppression (<50 copies/ml HIV RNA) at week 48 in individuals with previous NNRTIs virological failure and/or baseline transmitted resistance with the k103N resistance mutation, switching to DTG/RPV FDC. (Analysed in line with FDA snapshot) b. Virological failure will be 2 consecutive viral loads >50 copies at least 2 weeks apart, investigated over 48 weeks.	**Secondary** a. Proportion of participants with plasma HIV-1 RNA <50 c/mL at week 24, 48 and 96. b. Changes in laboratory parameter from baseline c. Changes in renal markers, bone markers, and fasting lipids from baseline, week 24, 48 and 96. d. Resistance in failures (descriptive analysis) and baseline factors associated with failures. e. Changes in QoL and patient satisfaction from baseline. f. Number of participants with adverse events (AEs), Severity of AEs, and treatment discontinuations due to AEs. g. Number of potential DDIs avoided. h. Virological suppression (<200 copies/ml HIV RNA) at week 24, 48, 96 in individuals with previous NNRTIs virological failure and/or baseline transmitted resistance with the k103N resistance mutation, switching to DTG/RPV FDC. Analysed in line with FDA Snapshot method. i. Pre-dose plasma concentrations of DTG and RPV at week 4 (experimental arm only), 48 (experimental arm only) &96. Plus pre/post-dose (as appropriate) at early termination visit and /or in the event of virological failure, a post dose sample will be taken within 20-28 hours. j. Changes in cell associated virus using PBMC Illumina MiSeq sequencing at week 48 and week 96.

FUNDING AND SUPPORT

FUNDER (& COLLABORATOR)

KEY CONTRIBUTORS



LIST OF ABBREVIATIONS

Acronym	Description
ABC	Abacavir
ACR	Albumin: Creatinine Ratio
ACTG	AIDS Clinical Trial Group
AE	Adverse Event
ALT	Alanine Amino Transferase
ALT (SGPT)	Alanine transaminase (serum glutamic-pyruvic transaminase)
APR	Annual Progress Report
AR	Adverse Reaction
ART	Anti Retroviral
AST	Aspartate aminotransferase
AST (SGOT)	Aspartate Aminotransferase (serum glutamic-oxaloacetic transaminase)
AV Block	Atrioventricular Block
BL	Baseline
BMD	Bone Mineral Density
CA	Competent Authority
CAR	Current Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CI	Chief Investigator
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phospohokinase
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CVA	Cerebral Vascular Accident
DAIDS	The Division of AIDS
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board

DSUR	Development Safety Update Report
DTG	Dolutegravir
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFV	Efavirenz
EMEA	European Medicines Agency
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EVG	Elvitegravir
FCBP	Females of Childbearing Potential
FDA	Food and Drug Administration (United States of America)
FDC	Fixed-Dose Combination
FEV1	Forced Expiratory Volume in the first second
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HIV RNA	Human Immunodeficiency Virus Ribonucleic Acid
HLA	Human Leukocyte Antigen
HS CRP	High-Sensitivity C-reactive protein
HSR	Hyper Sensitivity Reaction
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INI	Integrase Inhibitors
INR	International Normalised Ratio (for blood clotting time)

INSTI	Integrase Strand Transfer Inhibitor
ISF	Investigator Site File
ISRCTN Number	International Standard Randomised Controlled Trials
IUD	Intrauterine Device
IUS	Intrauterine Hormone Releasing System
LDL	Low Density Lipoprotein
LLN	Lower limit of Normal
MA	Marketing Authorisation
MCH	Mean Cell Haemoglobin
MCV	Mean Cell Volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MS	Member State
NEAT ID	The European treatment network for HIV, hepatitis and global infectious diseases
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OCT-2	Organic Cation Transporter
OD	Once daily
PBMC	Peripheral Blood Monoclonal Cell layer
PCR	Protein: Creatinine Ratio
pH	Power of hydrogen
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
PRTD	Proximal Renal Tubule Dysfunction
PSRAEs	Suicidality-related adverse events
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QoL Q	Quality of Life Questionnaire
QP	Qualified Person
RAL	Raltegravir
RBC	Red Blood Cell

RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	Ribonucleic Acid
ROKC	Research Organsiation (KC) Ltd
RPV	Rilpivirine
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SERF	Safety Event Reporting Form
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDR	Drug Transmitted Resistance
TEN	Toxic Epidermal Necrolysis
TMF	Trial Master File
TMG	Trial Management Group
TPN	Total Parental Nutrition
TSC	Trial Steering Committee
ULN	Upper limit of Normal
USM	Urgent Safety Measure
VL	Viral Load
WBC	White Blood Cell
WK	Week
WOCBP	Women of Child-Bearing Potential

1. BACKGROUND & RATIONALE

HIV-1 infected patients that experience virological failure while on NNRTIs (EFV or NVP) with development of K103N mutation (+/- other NNRTIs and/or NRTIs mutations) are usually switched to a boosted PI-based regimen or other complex ARV combinations. The same is true for patients who need to start antiretroviral therapy and have acquired virus that is already resistant to antiretrovirals (drug transmitted resistance, TDR). These “second line” combinations are often associated with numerous issues that can have a potential impact on the quality of life (QoL) of these patients: high pill burden, high potential for drug-drug interactions (DDIs), persistent side effects and metabolic toxicity. Therefore, a simpler and better tolerated alternative 2nd line treatment option would be a useful tool for the clinical management of these patients.

Dolutegravir (DTG) is a well-tolerated 2nd generation integrase strand transfer inhibitor (INSTI) with a low metabolic impact and low DDI potential; rilpivirine (RPV) is a well-tolerated NNRTI not affected by the presence of the K103N mutation, characterised by a lower DDI potential and metabolic impact compared to other NNRTIs. Neither requires a PK boosting agent. The aim of this study is to assess the efficacy and tolerability of a dual combined therapy with DTG 50 mg OD + RPV 25 mg OD in virologically suppressed patients with previous virological failure with NNRTIs and having the clinically significant mutation K103N. Secondary objective of the study is to assess whether a simplification of the treatment in term of pill burden, long term metabolic toxicity and potential of DDI improves the QoL of the participants. The study will also evaluate DTG & RPV trough concentrations plus changes in cell associated virus.

1.1. Assessment and management of risk

Summaries of findings from both clinical and non-clinical studies conducted with DTG or RPV can be found in the IBs and product labels for each individual drug.

The following section outlines the risk assessment and mitigation strategy for DTG and RPV in this protocol. Where available, the approved country product label should be referenced. For other ART regimens the approved country product labels should be referenced. See section 7.2 for RSI details.

Table 1.0 : Outline of the risk assessment and mitigation strategy for this protocol

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] **Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information**		
DTG: Hypersensitivity reaction (HSR) and rash **RPV:** Rash	**DTG:** Hypersensitivity is a recognised risk with integrase inhibitors, including DTG. HSR were characterised by rash, constitutional findings, and sometimes organ dysfunction, including severe liver injury. Hypersensitivity has been observed uncommonly with DTG in clinical trials. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported. **RPV:** Based on the association between other NNRTIs (such as EFV and NVP) and severe rash, and some observations of grade 1 and 2 rashes with RPV in clinical studies, severe skin reactions are also considered a potential risk for RPV. In clinical trials with DTG/RPV FDC, the risk of HSR was low. Serious skin reactions have not been seen with DTG+RPV FDC in clinical trials.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for HSR and rash (Section 6.12). The subject informed consent form includes information on this risk and the actions subjects should take in the event of: 1) a HSR or associated signs and symptoms; or 2) developing any type of rash or skin abnormality. For Grade 3/4 rash, except where the etiology is clear and not associated with study drug or where there is a definitive diagnosis clearly attributable to a concomitant medication (and not to study drug) or to a concomitant infection, subjects must permanently discontinue study drug and be withdrawn from the study.
DTG & RPV: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with	Subjects meeting either of the following criteria during the screening period are excluded from participating. • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin) • Subjects with acute viral hepatitis • Subjects positive for Hepatitis B surface antigen (+HBsAg) at screening

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information		
	inadequate therapy for HBV co-infected subjects, are likely contributed to significant elevations in liver chemistries. **RPV:** Hepatic events have been reported in patients receiving a RPV containing regimen. Patients with underlying HBV, HCV, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of RPV. A few cases of hepatic toxicity have been reported in patients receiving a RPV containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Hepatotoxicity is considered a risk for both DTG and RPV. Based on clinical trial data, synergistic or additive hepatotoxicity is not expected with DTG + RPV FDC.	• Subjects with an anticipated need for HCV therapy during the study. Specific detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 6.13).
DTG & RPV: Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviours are common in HIV-infected patients. Depression including suicidal ideation and behaviours is a recognised risk for both the DTG and RPV components of the DTG/RPV FDC. **DTG**: Depression, including suicidal ideation and behaviours, has been reported with DTG, particularly in patients with a pre-existing history of depression or psychiatric illness. A possible class effect has been suspected for INI drugs as the other two marketed INIs (RAL and EVG) have suicidal ideation/behaviours as adverse reactions in their product labels. The psychiatric profile for DTG (including suicidality, depression, bipolar and	Subjects who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating. As a result of the elevated risk in the HIV- infected population, subjects should be monitored closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information		
	hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable compared with EFV- based regimens in clinical trials. The reporting rate for insomnia was statistically higher for blinded DTG+ abacavir/lamivudine (ABC/3TC) compared to EFV/TDF/FTC in study ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG. **RPV**: Depression, including suicidal ideation and behaviours, has also been reported with RPV. As with DTG, RPV insomnia and abnormal dreams have been commonly reported with RPV. No synergistic or additive effect on the risk of depression or suicidal behaviours is expected from the co-administration of DTG and RPV based on available clinical trial data. Although the incidence of depression or suicidal behaviour is expected to be higher in those with a previous history, the majority of patients with such a history are not expected to have a recurrence when treated with DTG + RPV FDC.	
DTG & RPV: Increased rates of virologic failure/ Observed Resistance	Virologically suppressed subjects switching from stable CAR to DTG + RPV may experience virologic failure/breakthrough and development of resistance. All antivirals are prone to the development of resistance in the setting of inadequate combination therapy and/or incomplete adherence to therapy. DTG + RPV FDC is also a new dual antiretroviral regimen which is different from current standard	Subjects will have HIV-1 RNA measured at each study visit. Management of subjects experiencing an increase in viral load is described in Section 6.16. DSMB review of data may be triggered as a result of continuous monitoring of protocol-defined virological withdrawal.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information		
	treatment regimens that contain three antiretroviral components. **DTG:** Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies supported the efficacy findings from earlier analyses and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve subjects. **RPV:** In Phase III clinical trials (pooled Week 96 analyses), 3.2% of patients in the RPV arm experienced virologic failure between Week 48 and Week 96 (2.3 % on EFV). DTG + RPV dual therapy has not been studied in patients with known or suspected resistance to integrase inhibitors or NNRTIs.	
DTG: Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 7.7 & 7.8).
DTG: Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. There has been no indication of an increased risk of renal dysfunction in clinical trials with the combination of DTG + RPV.	Specific detailed toxicity management guidance is provided for subjects who develop a decline in renal function or proteinuria (Section 6.15 & 6.16).
DTG: Creatine Phosphokinase (CPK) elevations	Grade 3 to 4 creatine phosphokinase (CPK) elevations were observed with DTG in clinical trials. Elevations were usually explained by exercise and were transient	Specific toxicity management guidance is provided for subjects who develop grade 3 or 4 elevations in CPK (see section 6).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information		
and rhabdomyolysis	and asymptomatic. However, as rhabdomyolysis and myositis are labelled for raltegravir, this is considered a potential risk for DTG. Arthralgia and myalgia are labelled for DTG. No cases of rhabdomyolysis were reported in clinical trials with DTG +RPV FDC.	
DTG: Neural tube defects	In a birth surveillance study conducted in Botswana (the Tsepamo study), preliminary results showed that in babies born to women who were taking DTG when they became pregnant there was an increased risk of neural tube defects compared with the background rate. Later data from the study has shown a numerically higher rate of neural tube defects with exposure to DTG (0.19%) compared to non-DTG-containing antiretroviral regimens at the time of conception (0.11%), however, the difference was not statistically significant. A causal relationship of these events to the use of dolutegravir has not been established. No increased risk of these defects was reported in babies born to mothers who started dolutegravir containing regimen later in pregnancy. Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofoetal development studies. No adverse development outcomes, including neural tube defects, were identified. In reproductive toxicity studies in animals, DTG was shown to cross the placenta. Data analysed to date from other sources including the Antiretroviral Pregnancy	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, 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 until the last dose of study medication and completion of the Follow-up visit. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded; 3. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. Pregnancy status is monitored every 4 weeks throughout the study.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/RPV FDC] **Refer to individual IBs for DTG and RPV and the Juluca SmPC for additional information**		
	Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with DTG.	
RPV: QT interval (QTc) prolongation and overdose	In healthy subjects, supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (ECG). RPV at the recommended dose of 25 mg administered once daily is not associated with a clinically relevant effect on QTc and accidental overdose would not be expected to have a significant effect. However, there is a potential that intentional overdose of large quantities of DTG + FTC FDC could lead to a clinically significant prolongation of the QT interval.	Subjects who use medications which are associated with a known risk of Torsade de Pointes are excluded. Screening ECG performed to identify those with pre-existing prolonged QT interval.
DTG: Pancreatitis	**DTG**: Pancreatitis is considered a potential risk for the DTG component of the DTG+ RPV FDC. Lipase elevations are seen in HIV patients, with and without ART, and were noted in ART naive subjects from the Phase IIb and III studies with DTG. In clinical studies with DTG + RPV, one patient was reported as having acute pancreatitis. However, this was a grade 4 increase in lipase with no evidence of clinical pancreatitis, which resolved within 3 days and did not lead to withdrawal. There were no cases of pancreatitis in the CAR group. Lipase elevations may occur in patients treated with DTG + RPV FDC but are expected to be transient and not result in a diagnosis of pancreatitis.	Patients should be managed as routine standard of care.

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Primary objective

- To compare viral load outcomes on DTG/RPV FDC regimen (experimental arm) to continued ART regimen (control arm) at 48 weeks as measured by HIV-1 RNA below or confirmed above 50 copies/Ml.

2.2 Secondary objectives

- To investigate whether switching patients to DTG/RPV FDC is associated with improvement of lipid profile, patient satisfaction, quality of life and potential for drug-drug interactions, investigated over time through 96 weeks with evaluation (and comparison to control arm) at week 24, 48 and 96.
- To evaluate DTG & RPV trough concentrations
- Changes in cell associated virus (using Peripheral Blood Monoclonal Cell (PBMC) analysis)

2.3 Outcome measures/endpoints

2.3.1 Primary endpoint/outcome

- Virological suppression (<50 copies/ml HIV RNA) at week 48 in individuals with previous NNRTIs virological failure and/or baseline transmitted resistance with the K103N resistance mutation, switching to DTG/RPV FDC. Analysed with FDA snapshot.
- Virological failure will be 2 consecutive viral loads >50 copies at least 2 weeks apart, investigated over 48 weeks.

2.3.2 Secondary endpoints/outcomes

- Proportion of participants with plasma HIV-1 RNA <50 c/mL at week 24, 48 and 96.
- Changes in laboratory parameter from baseline.
- Changes in renal markers, bone markers, and fasting lipids from baseline at week 24, 48 and 96.

- Resistant outcomes in failures (descriptive analysis) and baseline factors associated with failure i.e. treatment emergent mutations (NRTI, NNRTI, PI and II regions) as compared with previous resistance tests.
- Changes in QoL and patient satisfaction from baseline.
- Number of participants with adverse events (AEs), severity of AEs, and treatment discontinuations due to AEs.
- Number of potential DDIs avoided (This will be measured by comparing the drug interaction outcomes between antiretroviral therapy and co-medications before and after the switch by using the www.hiv-druginteractions.org/ website (within the same study arm and between study arms). The grading will be done by looking at how many interactions graded amber or red will be graded green after the switch. For example, if a patient on atorvastatin as a co-medication and on two NRTIs and darunavir/cobicistat he would score "one amber and two green" and when switched to rilpivirine/dolutegravir, he would score "all green", showing the latter regimen is more favourable in terms of drug-drug interactions).
- Virological suppression (<200 copies/ml HIV RNA) at week 24, 48, 96 in individuals with previous NNRTIs virological failure and/or baseline transmitted resistance with the k103N resistance mutation, switching to DTG/RPV FDV. Analysed in line with FDA Snapshot method.
- Pre-dose plasma concentrations of DTG and RPV at week 4 (experimental arm only), 48 (experimental arm only) & 96. Plus pre/post-dose (as appropriate) at early termination visit and /or in the event of virological failure (see section 6.12) a post dose sample will be taken within 20-28 hours.
- Changes in cell associated virus using PBMC Illumina MiSeq sequencing at week 48 and week 96.

2.4 Exploratory endpoints/outcomes

- Changes in HsCRP over 96 weeks with evaluation at week 24, 48 & 96.
- Changes in CD4/CD8 over 96 weeks with evaluation at week 24, 48 & 96.

3 TRIAL DESIGN

Open-label, randomised, 2 arm, multicentre trial over 96 weeks with early or delayed switch from an ARV regimen containing a boosted PI (and/or other antiretroviral combinations) to Dolutegravir (DTG) & Rilpivirine (RPV) combination therapy in patients with a history of virological failure with NNRTIs or baseline drug transmitted resistance and having developed a K103N mutation.

Patients will be randomised to switch at baseline or at 48 weeks.

Study visits will take place at screening, baseline, weeks 4, 12, 24, 48, 52, 72, 96, and either a follow-up visit (30 days (+/- 7 days) after week 96 visit) or an early termination visit. An optional visit at week 60 may be performed for subjects on the control arm (3 months after therapeutic modification) as required per national guidelines

Routine investigations will include viral load, CD4 & CD8, haematology (including haemoglobin, white cell count and differential, platelets), biochemistry (including sodium, potassium, creatinine, albumin, glucose, ALT, AST, ALP, total bilirubin, total cholesterol, HDL, LDL, triglycerides), PK, PBMC, quality of life questionnaires (EuroQoL), patient satisfaction questionnaire, Pittsburgh sleep questionnaire, DDI assessment & urine sample (for haematuria, proteinuria, glycosuria, leukocytes) for full list of investigations please see appendix 1.

3.1 Study Schema

Control Arm

Experimental Arm

Figure 1.0

4 STUDY SETTING

This study will be conducted within the NEAT ID network and include sites in 7 countries that have an excellent track record in clinical research. A full feasibility assessment will be undertaken for all potential sites. A Trial Management Team will facilitate the project. See section 9 & 12 for details of DSMB composition and responsibilities.

The sponsor will perform site visits to assess protocol issues, consent, project management, data quality, drug dispensing, and trial management quality performance.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patient volunteers who meet all of the following criteria are eligible for this trial:

1. Is male or female aged 18 years or over.
2. Has documented HIV-1 infection.
3. Is capable of giving informed consent.
4. Is willing to comply with the protocol requirements.
5. Virologically suppressed (plasma HIV-RNA <50 copies/mL) and on a stable regimen for >24 weeks.
6. Subjects are required to have a history of the K103N mutation (acquired or selected). Subjects who at any time have had the mutations 100I, 101E/P, 106A/M, 138K/G/Q, 181C/I/V, 188L, 190A/S/E/Q, 230L mutations are to be excluded. Other NNRTI region variants can be included. All PI and NRTI mutations are acceptable. Study sites may ask the coordinating centre for advice as required.
7. Subjects must have never failed INSTI (2 x VL >200 >2 weeks apart) but current regimen can include INSTI.
8. A female, may be eligible to enter and participate in the study if she:

   is of non-child-bearing potential defined as post-menopausal (12 months of spontaneous amenorrhea without an alternative medical cause and ≥ 45 years of age). A high follicle stimulating hormone (FSH) level consistent with postmenopausal status may be used to confirm a post-menopausal state in women who are not using hormonal contraception) or hormonal replacement therapy at the discretion of the PI. However, in the absence of 12 months of amenorrhea, a single FSH measurement alone is insufficient.

   OR is physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or,

   OR is of child-bearing potential with a negative pregnancy test at Screening (& baseline visit) and agrees to use one of the following methods of contraception to avoid pregnancy:

   - True abstinence from penile-vaginal intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all study medications (When this is in line with the preferred and usual lifestyle of the subject.) (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and

withdrawal are not acceptable methods of contraception];

- Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion, see Appendix 3 for an example listing of approved IUDs);
- Male partner sterilisation confirmed prior to the female subject's entry into the study, and this male is the sole partner for that subject;
- Approved hormonal contraception (see appendix 4 for a listing of examples of approved hormonal contraception);
- Any other method with published data showing that the expected failure rate is <1% per year;
- Any contraceptive method must be used consistently and for at least 2 weeks after discontinuation of IP.

9. If a heterosexually active male, he is using effective birth control methods and is willing to continue practising these birth control methods during the trial and until follow-up visit.
10. Subjects currently receiving DTG or RPV, but not both, can be included.

5.2 Exclusion criteria

Patients meeting 1 or more of the following criteria cannot be selected:

1. Infected with HIV-2.
2. Detectable HIV-1 RNA at screening (HIV-1 RNA measurement >=50 c/mL).
3. Subjects requiring regular dosing doing with H2 or PPI antacid medications or a history of achlorhidria or drug known to interact with RPV or DTG.
4. Use of medications that are associated with Torsades de Pointes.
5. Corrected QT interval (QTc [Bazett]) >450 milliseconds or QTc (Bazett) >480 milliseconds for participants with bundle branch block. The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB).
6. Unstable health conditions (i.e. opportunistic infections, cancers, unstable liver disease etc).
7. Any evidence of an active Centres for Disease Control and Prevention Category C disease. Exceptions include cutaneous Kaposi's sarcoma not requiring systemic therapy and historic CD4+ lymphocyte counts of <200 cells/millimeter^3.

8. History or presence of allergy 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 intraepithelial neoplasia; other localised malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject prior to randomisation.
10. Any pre-existing physical or mental condition which, in the opinion of the Investigator, may interfere with the subject's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participants. Subjects considered to pose a significant risk of suicide should be excluded.
11. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the subject unable to take oral medication.
12. Using any concomitant therapy disallowed as per the reference safety information and product labelling for the study drugs. Specifically, co-administration with the following medicinal products is not allowed:
    - dofetilide or pilsicainide;
    - fampridine (also known as dalfampridine);
    - carbamazepine, oxcarbazepine, phenobarbital, phenytoin;
    - rifampicin, rifapentine;
    - proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole;
    - systemic dexamethasone, except as a single dose treatment;
    - St John's wort (*Hypericum perforatum*).
13. Has acute viral hepatitis including, but not limited to, A, B, or C.
14. Active hepatitis B/ Hep B non-immune subjects who have failed vaccination (antibody concentration < 10 international units). (If local practice does not include vaccination of low risk patients, then the patients without HBsAb are not excluded – this must be clearly documented in the medical records and eCRF). Note: subjects can be re screened if they receive vaccination and subsequently meet eligibility criteria.
15. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), and Hepatitis B surface antibody (HBsAb)

as follows: Participants positive for HBsAg are excluded; Participants positive for anti-HBc (negative HBsAg status) and negative for HBsAb are excluded (if local practice does not include vaccination of low risk patients, then the patients without HBsAb are not excluded – this must be clearly documented in the medical records and eCRF). Note: Subject positive for anti-HBc (negative HBsAg status) and positive for HBsAb are immune to HBV and are not excluded.

16. Participants with an anticipated need for any Hepatitis C virus (HCV) therapy during the Early Switch Phase and for interferon-based therapy for HCV throughout the entire study period.
17. Any investigational drug within 30 days prior to the trial drug administration.
18. Any evidence of viral resistance different to the one described in the inclusion criteria i.e. not meeting inclusion criteria or having different mutation at K103.
19. Dialysis or renal insufficiency (creatinine clearance < 50ml/min).
20. History of decompensated liver disease (Alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN), OR ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
21. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
22. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification (see appendix 4).
23. Opportunistic infection within 4 weeks prior to first dose of DTG plus RPV.
24. Clinical decision that a switch of antiretroviral therapy should be immediate.
25. Screening blood result with any grade 3/4 toxicity according to Division of AIDS (DAIDS) grading scale, except: asymptomatic grade 3 glucose, amylase or lipid elevation, asymptomatic grade 4 triglyceride elevation (re-test allowed) or unconjugated hyperbilirubinaemia due to atanazavir exposure.
26. Any condition (including illicit drug use or alcohol abuse) or laboratory results which, in the investigator's opinion, interfere with assessments or completion of the trial.
27. Women planning pregnancy or who are pregnant or breast feeding. (NB: See section 6.12 Withdrawal Criteria for guidance if pregnancy does occur).
28. Females of childbearing potential and males must be willing to use a highly effective (acceptable effective contraceptive measures are only acceptable for IMP's with unlikely human teratogenicity /

fetotoxicity in early pregnancy) method of contraception (hormonal method of birth control; true abstinence). Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods (see Appendix 4). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progesteron-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- true sexual abstinence

(NB: See section 6.12 Withdrawal Criteria for guidance if pregnancy does occur).

29. Hypersensitivity to the active substances or to any of the excipients listed below:

List of excipients

Tablet core

- Mannitol (E421)
- Magnesium stearate
- Microcrystalline cellulose
- Povidone (K29/32)
- Sodium starch glycolate
- Sodium stearyl fumarate
- Lactose monohydrate
- Croscarmellose sodium
- Povidone (K30)
- Polysorbate 20
- Silicified microcrystalline cellulose

Tablet coating

- Polyvinyl alcohol- part hydrolysed
- Titanium dioxide (E171)
- Macrogol
- Talc
- Iron oxide yellow (E172)
  Iron oxide red (E172)

6 TRIAL PROCEDURES

The schedule of assessments is summarised in the study flow chart in Appendix 1. From the Baseline visit through to follow up, visits may take place +/- 7 days from that specified at the discretion of the Investigator.

Please note that if additional tests / procedures are required in accordance with local practice then these should still be performed (no usual tests / procedures should be withheld from the patients during the study).

6.1 Recruitment

Following full written informed consent, sites must keep a record of all screening and enrolled participants using screening and enrolment logs. Diagnostic tests/procedures may be used in determining eligibility however, written informed consent must be obtained prior to any study specific procedures. All information collected for eligible participants will be completely anonymised and recorded in the Investigator Site File (ISF).

6.2 Study Registration

All eligible consented participants will be given a unique study identifier via an electronic study database.

Anonymised information that will be collected are:

- age,
- gender,
- ethnicity
- whether the patient is enrolled or not enrolled,
- the reason not eligible for trial participation, or if they are eligible but declined (where available) Reason for subject wishing to participate

6.3 Patient identification

Patients will be identified through clinic visits by their direct study medical care team and visits will be captured on a participant screening log.

6.4 Screening

Written informed consent must be obtained from the subject prior to performing any study related evaluations or procedures.

Subjects will be provided with written information about the study in the form of a Participant Information Sheet (PIS) and will be allowed adequate time for questions and to consider the study before agreeing to participate. It will be the responsibility of the investigator or co-investigator to obtain written informed consent prior to undertaking any procedures detailed in the protocol. This responsibility may be delegated to other suitably trained personnel if allowed according to country-specific regulations and approved by the local ethics committee.

The investigator or designee must provide adequate explanation of the aims, methods, objectives, and potential hazards of the study. It must also be explained to the subject that they are free to refuse or withdraw from the study for any reason without detriment to their future care or treatment.

The following evaluations must be performed within 28 days prior to study randomisation:

- Assessment of subject eligibility according to the inclusion and exclusion criteria
- Demographics
- Medical and social history (past and current), including HIV-associated conditions (see Appendix 1)
- Full antiretroviral history (including resistance history i.e. record all resistance history by major mutations in NRTI, NNRTI, PI and II regions).
- Review of non-antiretroviral medication (any medication taken within the last 30 days)
- Concomitant medication check
- Physical examination including height and weight
- Vital signs (pulse, blood pressure): after 10 minutes resting
- Urinalysis (see Appendix 1) and pregnancy test for WOCBP (β-HCG).
- Laboratory evaluations (non-fasting): haematology and biochemistry (Appendix 1)
- Total cholesterol and lipids (HDL, LDL and triglycerides)
- HIV RNA viral load

- HBV antigen test (including HbsAG, anti-HBc and HBsAb , if done as per standard practice) and HCV antibodies test (if test positive for HCV antibodies, test for HCV RNA, if positive and chronic for either HBV or HCV, add AST test to the biochemistry panel at screening visit. Hep B surface antibodies post vaccination levels to be included in assessment, if this is part of local practice)
- ECG
- CD4 & CD8 count / % and ratio

6.5 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-side standard routine care at the participating site (including the collection of identifiable participant data unless the trial has prior approval from the Ethics Committee (EC). The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The Principal Investigator takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a

participant's behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing PIS in other languages or in a format easily understood by the participant population (in the case of cognitive impairment).

6.6 Randomisation

6.6.1 The randomisation scheme

This study is open label and patients will be randomised to switch at baseline or after 48 weeks. Full details of randomisation scheme will be included in the study randomisation plan.

6.6.2 Method of implementing the allocation sequence

Method will be detailed in the randomisation plan.

6.6.3 Blinding

This section is not applicable.

6.6.4 Unblinding

This section is not applicable.

6.7 Baseline data

The following evaluations and procedures are to be completed pre dose.

- Smoking history
- Alcohol intake
- Recreational drug use
- Symptoms review and adverse events
- Review of concomitant medications
- Physical examination (symptom directed)
- Weight
- Vital signs (pulse, blood pressure: after 10 minutes resting)
- Urinalysis (see Appendix 1)
- Laboratory evaluations: haematology and biochemistry (fasted) (Appendix 1)

- Total cholesterol and lipids (HDL, LDL and triglycerides) (fasted)
- HIV RNA viral load as per local laboratory standard method.

  Note. In event of viral load failure follow section 6.18 viral failure, resistance assessment & pharmacokinetic assessment procedures.
- Blood sampling for PBMC isolation

  (Required unless exemption documented in site contract i.e. if site does not have capacity to process PBMC samples)
- CD4 & CD8 count / % and ratio.
- Quality of life questionnaire (EuroQoL)
- Pittsburgh sleep questionnaire
- Patient treatment satisfaction questionnaire
- DDI assessment
- Drug dispensing
- Adherence assessment
- Pregnancy test for WOCBP (β-HCG).

  Note: Investigators to remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements. As a reminder, females of reproductive potential who changed their minds and desire to be pregnant should be withdrawn from the study.

  Note: all subjects should be reminded to take precautions to prevent transmission of HIV in accordance with national guidelines.

See Appendix 1 for details of assessments required.

6.8 Study on treatment visits

Study Visits: weeks 4, 12, 24, 48, 52, 72 and 96 (all visits +/- 7 days visit window). An optional visit at week 60 may be performed for subjects on the control arm (3 months after therapeutic modification) asrequired per national guidelines. The following evaluations and procedures are to be performed pre dose:

- Symptoms review and adverse events
- Review of concomitant medications
- Physical examination (symptom directed)

- Weight
- Vital signs (pulse, blood pressure: after 10 minutes resting)
- Viral load
- Alcohol intake, smoking habit and recreational drug use (week 24, 48 and 96)
- Adherence assessment (including date/time of last dose on PK days including ETV visit and/or in the event of virological failure)
- Urinalysis (see Appendix 1) (week 24, 48 and 96)
- Week 48 (and screening) only: HBV antigen test (including HbsAG, anti-HBc and HBsAb, if done as per standard practice) and HCV antibodies test (if test positive for HCV antibodies, test for HCV RNA, if positive and chronic for either HBV or HCV, add AST test to the biochemistry panel at screening visit. Hep B surface antibodies post vaccination levels to be included in assessment, if this is done as per local practice)
- Laboratory evaluations: haematology and biochemistry (fasting)
- Total cholesterol and lipids (HDL, LDL and triglycerides) (fasted)
- PBMC (BL & week 48, 96 & ETV only)
  (Required unless exemption documented in site contract i.e. if site does not have capacity to process)
- Pre-dose blood sampling for measurement of DTG & RPV (PK assessment) (week 4 & 48 (experimental arm), week 52 (deferred switch patients) and week 96 (both arms)). Plus pre- or post-dose (as appropriate) at early termination visit and/or in the event of virological failure (see section 6.12). A post dose sample will be taken within 20-28 hours
- HIV RNA viral load
  Note. In event of viral load failure follow section 6.18 viral failure & resistance assessment procedures.
- CD4 & CD8 count / % (week 24, 48, 72 and 96)
- EuroQoL questionnaire (week 24, 48 and 96)
- Pittsburgh sleep questionnaire (week 24, 48 and 96)
- Patient treatment satisfaction questionnaire (week 24, 48 and 96)
- DDI assessment (week 24, 48 and 96)
- Adherence assessment
- Drug Dispensing (not at week 96)

- Pregnancy test for WOCBP (β-HCG).

  Note: Investigators to remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements. As a reminder, females of reproductive potential who changed their minds and desire to be pregnant should be withdrawn from the study.

  Note: all subjects should be reminded to take precautions to prevent transmission of HIV in accordance with national guidelines

- In addition urine home pregnancy tests for WOCBP should be performed by the patient every 4 weeks. The results should be communicated via a telephone call visit and recorded in the patient records and in the eCRF.

All subjects should return unused DTG+RPV tablets at next clinic visits for drug accountability purposes. The investigator or designee is responsible for keeping accurate up-to-date accountability documentation for the study drugs (as per pharmacy manual) such as dispending, returns, and supply.

See Appendix 1 for details of assessment and specific visit requirements.

6.9 Follow-up assessments

This visit will be conducted by phone 30 days post the week 96 visit (+/- 7 day window). The following evaluations are to be performed:

- Symptoms review and adverse events
- Urine home pregnancy test for WOCBP. The result should be communicated via a telephone call visit and recorded in the patient records and in the eCRF.

A follow-up visit is not required if a patient withdraws from IMP prior to week 96. In this case, an early termination visit should be conducted instead. See section 6.10.

6.10 Early Termination visit

In the case of early termination, every attempt will be made to ensure the subject has a termination visit. At this visit, the following evaluations and procedures are to be performed:

- Symptoms review and adverse events
- Alcohol intake, smoking habit and recreational drug use
- Total cholesterol and lipids (HDL, LDL and triglycerides) (fasted)

- PBMC (Required unless exemption documented in site contract i.e. if site does not have capacity to process).
- Blood sampling for measurement of DTG & RPV (PK assessment). (Pre- or post-dose (as appropriate) at early termination visit and/or in the event of virological failure (see section 6.18). A post dose sample will be taken within 20-28 hours.
- Vital signs (pulse, blood pressure: after 10 minutes resting)
- Physical examination (symptom-directed)
- Weight
- Review of concomitant medications
- Laboratory evaluations: haematology and biochemistry (fasting) (Appendix 1)
- HIV RNA viral load
  - Note: In event of viral load failure follow section 6.18 viral failure & resistance assessment procedures.
- CD4 & CD8 count /%
- EuroQoL questionnaire
- Pittsburgh sleep questionnaire
- Patient treatment satisfaction questionnaire
- DDI assessment
- Adherence assessment (including date/time of last dose on PK days including ETV visit and/or in the event of virological failure)
- Pregnancy test for WOCBP (β-HCG).

Patients will be requested to attend for remaining visits and complete study assessments to week 96 even if they are no longer taking study medication.

See Appendix 1 for details of assessments.

6.11 Qualitative assessments – Nested studies

This section is not applicable

6.12 Withdrawal criteria

A subject is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons

of medical prudence, to stop study medication. 15% lost to follow-up rate expected.

All patients who discontinue study medication will be followed up and requested to attend for study visits up until week 96.

If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study and the reason for withdrawal recorded in the Case Report Form.
If any participants experience virological failure (two consecutive HIV-RNA more than 50 copies/ml), the study medication must be stopped and participants should be managed in accordance with local processes, participants will be followed up and asked to attend all study visits.

Study medication may also be discontinued in the following instances:
1. If the subject withdraws their consent.

2. If the investigator considers in the interest of the subject (i.e. intercurrent illness, unacceptable toxicity) that it is best for them to stop study medication.

3. The subject fails to comply with the protocol requirements or fails to cooperate with investigator.

The date and reasons for stopping medication will be clearly stated on the subject's CRF and source document. Every attempt should be made to arrange follow up visits for subjects who are withdrawn from study medication. This visit should involve assessments as outlined in section 6.

A female subject receiving dolutegravir/rilpivirine who becomes pregnant during the study should remain on study for the purpose of follow-up but must immediately have their dolutegravir/rilpivirine withdrawn and replaced by triple standard ARV therapy to avoid suboptimal drug exposure during pregnancy. Exceptions may be discussed with ViiV in situations where the benefits of continuing the pregnant woman on dolutegravir plus rilpivirine outweigh the risks. For reporting requirements for pregnancies see section 8.3.

Note: Investigators must remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements. Females of reproductive potential who changed their minds and desire to be pregnant should be withdrawn from the study.

Allergic reactions

Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the investigational product(s) should permanently discontinue the investigational product regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

Subjects in the CAR arm who are receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information for ABC.

Rash

Mild to moderate rash is an expected adverse reaction for both DTG and RPV containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. The index case of hypersensitivity with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiform, have been reported for DTG, RPV or DTG/RPV FDC in clinical trials.

Subjects with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Subjects may continue study drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥ 2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Subjects should permanently discontinue study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as adverse events (see section 8) and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings).
If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

Subjects in the CAR arm who are receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information for ABC.

Subjects withdrawing from the trial may be replaced if considered necessary by the Chief investigator.

6.13 Liver Chemistry Stopping and Follow up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study drug and the follow-up period. Study drug must be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin; bilirubin fractionation required)

NOTE: serum bilirubin fractionation should be 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 meets liver stopping criteria and should be reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- ALT ≥8xULN;
- ALT ≥3xULN (if baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8 xULN that persists > 2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks;

Subjects who develop ALT ≥5xULN should be followed weekly until resolution or stabilisation (ALT <5xULN on 2 consecutive evaluations).

When liver chemistry stopping criterion is met, the following procedures must be followed:

- **Immediately** hold dolutegravir and rilpivirine. If a causal relationship between the liver event and dolutegravir and rilpivirine cannot be ruled out, then doluetgravir and rilpivirine must be permanently discontinued and the Subject not rechallenged due to the risk of a recurrent reaction. If the liver event has a clear underlying alternative cause, other than drug-induced liver injury, then Drug Restart may be considered (see below).
- Report the event to the study sponsor pharmacovigilance team within 24 hours of learning its occurrence (see section 8.3)
- Events of possible drug-induced liver injury (DILI) with hyperbilirubinemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) will be reported to the Sponsor as SAEs using the SAE reporting form Complete the liver event CRF for all events meeting liver stopping criteria.

- Perform liver event follow up assessments (described below), and monitor the subject until liver chemistries resolve, stabilise, or return to baseline values as described below;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring;
- A specialist or hepatology consultation is recommended;
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values;

Consider the following additional tests to further evaluate the liver event:

- Viral hepatitis serology including:
    - Hepatitis A IgM antibody;
    - HBsAg and Hepatitis B Core Antibody (IgM);
    - Hepatitis C RNA;
    - Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening
- Drugs of abuse screen including alcohol
- Serum acetaminophen test (APAP adduct test)
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease;

- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.

Restarting Study Drug

If a causal relationship between the liver event and DTG/RPV FDC cannot be ruled out, then DTG/RPV FDC must be permanently discontinued and the Subject not rechallenged.

Drug Restart Following Transient Resolving Liver Events Not Related to Study Drug

Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT<3xULN) where:

- Liver chemistries have a **clear underlying cause** other than drug-induced liver injury (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury.
- The subject is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from the Chief Investigator plus Ethics Committee/IRB & ViiV Healthcare (as appropriate) for the drug restart has been obtained.
- The subject has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death.
- The subject has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file.
- Following drug restart, the Subject will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

6.14 Suicidal Risk Monitoring

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation

and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor subjects for suicidality before and during treatment.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

See section 8 for reporting details.

6.15 Decline in Renal Function

Subjects who experience an increase in creatinine from Baseline of 45 mMol/L (or 0.5 mg/dL) without associated evidence for proteinuria should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio should be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the sponsor to discuss additional follow-up and medical management.

Subjects who have a decline in creatinine clearance of >50% must return for a confirmatory assessment as soon as possible. A urinalysis and urine microalbumin/creatinine ratio should be done at this confirmatory visit. If the estimated creatinine clearance has declined by >50% (confirmed), then study medication should be withheld and the investigator should contact the sponsor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g. NRTI background therapy, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If a subject in the control group is also receiving TDF, then a switch to an alternative fully active NRTI should be considered if restarting study medication. Current local prescribing information should be consulted for additional details on dosing background therapy in renally impaired subjects. If study medication is reinitiated, it should have been withheld for no more than 4 weeks. If IP is not reinitiated the subject must be withdrawn.

Proximal Renal Tubule Dysfunction (PRTD) is defined as:

- Confirmed rise in serum creatinine of ≥0.5mg/dL from baseline AND serum phosphate <2.0mg/dL;
- Either of the above accompanied by any two of the following:

- Glycosuria (≥250mg/dL) in a non-diabetic;
- Low serum potassium (<3mEq/L);
- Low serum bicarbonate (<19mEq/L).

Subjects meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks. A urinalysis should be done at the time of the confirmatory assessment. If PRTD is confirmed the drugs should be terminated and the sponsor should be contacted to discuss the rationale for restarting study drugs (if appropriate). If a subject is also receiving TDF/FTC, then a switch to an alternative NRTI combination should be considered if restarting study medication. If re initiation of study medication is planned, study medication should be withheld for no more than 4 weeks. Subjects on ABC/3TC FDC may switch to the individual components dose adjusted for renal dysfunction according to approved prescribing information, or switch to alternative nucleosides at the discretion of the Investigator.

6.16 Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (>0.3mg/mg, >300mg/g or >34mg/mmol) that represents a change from baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be made for additional evaluation after consultation with the sponsor. Additional evaluation may include a creatinine measurement and nephrology referral.

Subjects with an abnormal urine albumin/creatinine ratio (>0.3mg/mg, 300 mg/g or>34mg/mmol and representing a change from baseline) and a serum creatinine increase >45 mMol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study sponsor should be immediately contacted. Agreement on further management should be agreed between the investigator and study sponsor.

6.17 Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study drug, study drug should be discontinued and the subject withdrawn from the study.

6.18 Storage and analysis of samples

See appendix 1 for details of assessments required.

All samples (with the exception of PK & PMBC samples) will be analysed at each local site laboratories and destroyed after analysis. PK samples will be shipped and analysed by a central laboratory in the UK. PBMC samples will be shipped and analysed by a central laboratory in Spain.

Collection and processing and storage instructions for all samples will be detailed in a separate Laboratory Manual.

6.19 Virological failure

Virological failure is defined as two consecutive measurements of plasma viral load above 50 copies/ml separated by at least 14 days during the assigned treatment. Note: If the initial sample analysis returns result of >50c/mL, the remainder of the sample should be re-analysed, if possible. Only if the repeat analysis produces a second result of >50c/mL, or if re-analysis is not possible, the patients should be recalled for retesting. The remainder of the retesting sample should be analysed if the retesting analysis produces a result of >50c/mL. In case of virological failure a resistance study will be conducted in the local lab of each centre. Note: resistance test should be performed from the suspect virological failure visit sample and from the confirmatory visit when available.

Pharmacokinetic testing should also be carried out in the event of viral failure.

Patients should discontinue study medication and receive rescue medication at investigators discretion.

Therapeutic failure includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death.

6.20 End of trial

The end of the trial is defined as the date of the last visit (i.e. Follow-up visit) of the last subjects undergoing the trial.

The sponsor must notify the Competent Authority and main REC of the end of a clinical trial within 90 days of its completion.

Note: The DSMB will elect stopping criteria as defined in the DSMB charter. If the study ends early by recommendation from the DSMB or for any other reason, the sponsor will notify the Competent Authorities and Ethics Committees of the reasons for the premature termination.

7 TRIAL MEDICATION

7.1 Name and description of investigational medicinal product(s)

Subjects will discontinue their usual boosted protease inhibitor or other ARV regimen (including Anatomical Therapeutic Chemical Classification System codes: JO5AB, JO5AE, JO5AF, JO5AG, JO5AR, JO5AX) and will switch to DTG plus RPV at baseline or week 48.

ViiV will supply Dolutegravir 50mg / Rilpivirine 25mg FDC tablets in the form of "Juluca"(which will be labelled in accordance with annex 13 requirements).

From baseline to week 96 or from week 48 to week 96, as randomised, participants will take a DTG/ RPV combined tablet once a day orally. Participants in the deferred group will continue to take their usual ARV regimen from baseline to week 48 until they switch to DTG/ RPV combined tablet.

The early switch group will be dispensed a supply of DTG/RPV combined tablets at baseline, week 4, 12 and 24. Both the early switch group and deferred switch group will be dispensed supply of DTG/RPV combined tablets at week 48, 52 and 72. Please refer to the study specific pharmacy manual for more information. Note, dispensing weeks may be modified with sponsor's approval and in line with local regulations (if required). Prior to switch subjects will continue to be dispensed standard care boosted protease inhibitor or other ARV regimen.

7.2 Reference Safety Information

The Reference Safety Information (RSI) for the DTG/RPV FDC is the Juluca Summary of Product Characteristics (section 4.8 Undesirable effects). Please refer to this for further information on contraindicated treatments, drug interactions and adverse events expectedness. For pre-switch reference

safety information, investigators are to refer to the SmPC (per ATC code) for information on expectedness, contraindicated treatments, drug interactions and adverse events.

7.3 Drug storage and supply

Investigators are to ensure that the investigational product will only be used in accordance with the protocol. Drug supplies will be kept in a secure, limited access storage area under the recommended storage conditions (see pharmacy manual) accessible only to those authorised by the investigator to dispense to eligible subjects.

The investigator will ensure that records are maintained showing the receipt and disposition of all study supplies. A drug accountability log will be kept with the investigational supplies for reconciliation purposes. This should be used to record the trial identification of the subject to whom the investigational product was dispensed, the date and quantity of investigational product dispensed, and the quantity of investigational product unused/returned by the subject. This will be verified by the study monitor.

Partially used or empty containers may be destroyed by pharmacy/designee at local site after the study monitor has completed a final inventory to verify the quantity returned. The pharmacy/designee are required to document destruction for verification by the sponsor.

7.4 Preparation and labelling of Investigational Medicinal Product

Dolutegravir & Rilpivirine combined therapy tablets will be labelled with Annex 13 compliant labels and QP certified by Almac Group Ltd who will provide supply directly to each site on request of the sponsor.

Boosted PIs (or other antiretroviral combination regimen) will be sourced from usual commercial supply as per standard practice.

Further information can be found in the pharmacy manual.

7.5 Dosage schedules

Experimental arm (Baseline visit switch group): One combined Dolutegravir 50mg /Rilpivirine 25mg tablet taken orally once daily (at the same time) for up to 96 weeks with a meal. NB: A high protein drink is not suitable substitute for a meal.

Control arm (deferred week 48 switch group): patients will continue their current boosted PI regimen (or other antiretroviral combination regimen) for 48 weeks. Patients will then be switched to one combined Dolutegravir 50mg /Rilpivirine 25mg tablet taken orally once daily for up to 48 weeks with a meal.

7.6 Dosage modifications

There are no dose modifications for this trial. Please refer to section 6 for withdrawal and stopping rules.

7.7 Known drug reactions and interaction with other therapies

Dolutegravir

See section 8.3 and reference safety information.

Dofetilide is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity. Strong inducers of DTG metabolism such as carbamazepine must be avoided.

Rilpivirine

See section 8.3 and reference safety information.

Medications that affect rilpivirine and that are affected by the use of rilpivirine accordingly must be reviewed by the investigator and/or avoided.

7.8 Concomitant medication

DTG/RPV FDC is contraindicated in combination with the following:

- antiarrhythmic agents dofetilide or pilsicainide (DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity)
- fampridine (also known as dalfampridine)
- anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- antimycobacterials rifampicin, rifapentine
- proton pump inhibitors (such as omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole)
- systemic dexamethasone (except as a single dose treatment)
- St John's wort (Hypericum perforatum)

7.9 Prior Concomitant Therapy

All medications (prescriptions or over-the-counter medications, herbal and naturopathic products) continued at the start of the treatment or started during the treatment must be documented (dose, frequency, stop and start dates). Unnecessary changes or additions to any concomitant medication should be avoided.

Warnings and precautions regarding contraindicated concomitant medications, AE and drug interactions can be found above or within reference safety information.

NOTE! Caution must also be applied when patients take medications that inhibit CYP3A as this may lead to excessive exposure of rilpivirine.

Any medications excluded in the Exclusion criteria will not be permitted in this study. However, if there is a clinical need for the use of any of these medications then the participant may need to be discontinued from the study. If this is the case, then the investigator should discuss with the CI or Sponsor trials team, but the final decision remains that of the site investigator.

All concomitant medication information will be captured in the participant's Case Report Forms.

7.10 Trial restrictions

Please refer to inclusion & exclusion criteria listed in sections 5.1 & 5.2.

7.11 Assessment of compliance

Adherence during the trial will be monitored by subject questioning regarding missed tablets at each visit. If poor adherence is suspected based on tablet counts, this will be discussed with the subject to confirm lack of adherence i.e. via subject interview. The outcome of this questioning should be documented in the patient notes. If the subject misses a significant number of tablets, this should be reported to the study monitor

All subjects should return unused medication and containers at weeks 72 and 96 (plus at weeks 4, 12, 24 and 48 for the experimental arm) for pharmacy accountability purposes (see section 7.3).

7.12 Provision of treatment after the end of the trial

No post trial medication will be provided to patients. Following study completion, patients are to receive treatment as per local standard of care.

8 PHARMACOVIGILANCE

8.1 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.
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 a trial medication 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 trial medication 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 • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: For the purposes of this study, all AEs meeting liver stopping criteria (as defined in section 6.13) associated with dolutegravir and all events of possible drug-induced liver injury (DILI) with hyperbilirubinemia defined as ALT ≥ 3Xuln and bilirubin ≥ 2Xuln (>35% direct) are also considered serious and must be reported (see Section 8.3) 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.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: The reference safety information for the DTG/RPV FDC is contained within Juluca Summary of Product Characteristics (SmPC) at section 4.8 Undesirable effects, please refer to this document for further information on contraindicated treatments, drug interactions and adverse events expectedness.

"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.

8.2 Operational definitions for (S) AEs

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study treatments. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or

not considered related to the medicinal (investigational) product.

Adverse events observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject's notes throughout the study. The nature of each event, time of onset after drug administration, duration and severity will be documented together with the Investigator's opinion of the causal relationship to the investigational product (unrelated, unlikely, possible, probable, and definite).

All subjects experiencing adverse events, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed.

Procedures such as surgery should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted on the CRF.

Planned procedures such as surgery pre planned prior to the subject's enrolment into the study do not need to be reported as adverse events if these are documented as planned at the screening visit.

Clinically significant changes in physical examination and blood safety profiles should also be recorded as adverse events.

8.2.1 Assessment of Intensity

Severity should be recorded and graded according to the AIDS Clinical Trial Group (ACTG) Grading Scale (*appendix 2*).

Note: There is a distinction between the seriousness and the intensity of an adverse event. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious adverse event. For example, a headache may be severe in intensity but would not be classified as serious unless it meets one of the seriousness criteria for serious events.

All events deemed to be Grade 4 (potentially life threatening) according to the ACTG grading scale should be

routinely reported as a serious adverse event. However, there may be occasions where in the investigator's clinical judgement they do not consider the event to be life threatening therefore they do not consider the event to meet the definition of an SAE. In these cases, the investigator must document clearly in the participants source documentation that the Grade 4 event has been assessed and why in their clinical judgement they do not consider the event to be life threatening.

8.2.2 Assessment of Causality

The relationship to study drug of each adverse event will be assessed using the following definitions:

DEFINITE: distinct temporal relationship with drug treatment. Known reaction to agent or chemical group or predicted by known pharmacology. Event cannot be explained by subject's clinical state or other factors.

PROBABLE: reasonable temporal relationship with drug treatment. Likely to be known reaction to agent or chemical group or predicted by known pharmacology. Event cannot easily be explained by subject's clinical state or other factors.

POSSIBLE: reasonable temporal relationship with drug treatment. Event could be explained by subject's clinical state or other factors.

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by subject's clinical state or other factors.

UNRELATED: the event occurs prior to dosing. Event or intercurrent illness is due wholly to factors other than drug treatment.

8.2.3 Collection and follow up of Adverse Events

All adverse events, however minor, will be documented in the CRF whether or not the Investigator considers the event to be treatment related.

The adverse event reporting period will be from consent until the subject's final study visit (I.e. follow-up visit or end of trial visit). In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as possibly, probably or definitely related to the study drug medication should also be reported as an Adverse Event.

Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit.

All adverse events should be followed up until they are resolved or the subject's participation in the study ends (i.e. until the final CRF is completed for that subject). In addition, all serious and non-serious adverse events assessed by the Investigator as possibly related to the investigational medication should continue to be followed until resolution, or until no further change can reasonably be expected.

Rash and any associated symptoms should be reported as adverse events (see section 6.12)

8.2.4 Serious Adverse Events (SAE) & reportable events

See SAE definition within section 8.1.

Liver stopping criteria & clinically significant liver chemistry evaluation adverse events.

All AEs meeting liver stopping criteria, clinically significant liver chemistry elevations (as defined in section 6.13) associated with dolutegravir and all events of possible drug-induced liver injury (DILI) with hyperbilirubinemia defined as ALT ≥ 3Xuln and bilirubin ≥ 2Xuln (>35% direct) are considered serious for the purposes of this clinical trial and must be reported. See section 8.4 for reporting guidelines. NOTE: bilirubin fractionation should be 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 should still be reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Suicidality-related adverse event

If any subject experiences a possible suicidality-related adverse event (PSRAE) while participating in this study that is considered by the Investigator to meet above described definitions, this should be reported to the Sponsor. See section 8.4 for reporting format & timeline. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator should exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide related.

Pregnancy

There is no requirement to report pregnancies in female partners of male participants. Please see risk section 1.1 for further details.

Trial subject pregnancies should be reported as per table 2

Overdose

All participants should be counselled about the importance of taking the medications as prescribed and they should understand the quantity of medicine they should be taking. Participants must be told to contact the clinic immediately if they take too much medication. If the overdose fits the criteria of an SAE (see Section 8) it should be reported appropriately. See table 2 for SAE reporting format and timelines.

Deaths

Any AE, adverse reaction or unexpected adverse reaction that results in death should be reported as an SAE. See table 2 for SAE reporting format and timelines.

Deaths occurring more than 28 days after the final dose, which are considered to be unrelated to the study medication, should not be reported as a Serious Adverse Event.

8.3 Recording and reporting of SAEs AND SUSARs

8.3.1 Reporting requirements

All SAEs occurring from consent to 28 days post cessation of trial treatment must be recorded & reported by site (see table 2 for forms to be used and reporting timeline).

The investigator must immediately and not later than in 24 hours, report to the sponsor; all serious adverse events by emailing [redacted] or by sending a fax to [redacted].

For each SAEs / SUSARs the following information will be collected in a dedicated safety event reporting form (SERF):

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be provided to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Query responses should be also provided to the Sponsor within the requested timelines. Follow-up information and Query Response must be sent emailing [redacted] or by sending a fax to [redacted]. Events will be followed up until the event has been resolved or a final outcome has been reached.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected, will be classified as SUSARs and will be subject to expedited reporting to the Competent Authority. The Sponsor will inform CAs, ECs and ViiV of SUSARs within the required expedited reporting timescales.

Table 2: Safety Reporting Format & Timelines

Safety Data	Reporting Format	Timeline
All SAEs arising during the Clinical Trial, regardless of Investigator/designee causality assessments against IMP(s)	SERF	Site to report to sponsor within 24 hours of first becoming aware of the event.

Pregnancy information for all female Clinical Trial Subjects who become pregnant while participating in the Clinical Trial and following exposure to an IMP.	SERF	Site to send to sponsor within 24 hours of first becoming aware of the pregnancy or the pregnancy outcome.
The subject will also be followed to determine the outcome of the pregnancy (including information on the status of the mother and child), which will also be reported to sponsor.		
All liver events meeting the criteria for an SAE, including all events of possible drug-induced liver injury (DILI) with hyperbilirubinemia defined as ALT ≥ 3Xuln and bilirubin ≥ 2Xuln (>35% direct)	SERF	The SAE form must be completed and reported to the sponsor within 24 hours.
All Liver Chemistry Elevations that meet Liver Stopping Criteria (as defined in the Protocol), regardless of Investigator/designee causality assessments against IMP(s); and whether or not the event and/or associated signs and symptoms meet definitions of seriousness as outlined above	Liver Event CRF Modules i.e. VHL liver event CRF, liver imaging and/or liver biopsy CRFs	Site to complete the Liver event CRF modules and send to sponsor within one week of first becoming aware of the event

Suicidality-related adverse events (PSRAEs) (as defined in the Protocol) that met the criteria for an SAE.	SERF PSRAE CRF Module	The SAE form must be completed and reported to the sponsor within 24 hours. The PSRAE CRF Module should be completed and reported to the sponsor within one week of the investigator diagnosing a possible suicidality-related adverse event
Deaths	Any AE, adverse reaction or unexpected adverse reaction that results in death should be reported as an SAE on an SERF	Site to report to sponsor within 24 hours of first becoming aware of the event.
Overdose	If the overdose fits the criteria of an SAE (see Section 8) it should be reported appropriately on an SERF	Site to report to sponsor within 24 hours of first becoming aware of the event.

All safety reports and reportable events listed on the above table (including Investigator causality) assessment should be reported in English to the sponsor.

Reporting Period

The SAEs, and pregnancy reports that are subject to the above reporting provisions are those that occur following the consent through to 28 days post cessation of trial treatment.

8.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor

if a record of receipt is not received.

3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit.
3. Reporting safety information to the Data Safety Monitoring Board (DSMB) according to committee charter documents.
4. Expedited reporting of SUSARs to the Competent Authorities and ECs within required timelines in accordance with the applicable country legislations.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for and notifying PIs of updates to the Reference Safety Information for the trial.
7. See section 8.3.1 for details of reporting requirements to ViiV.

Data Safety Monitoring Board (DSMB):

In accordance with the DSMB Charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

8.5 Reporting urgent safety measures

It is the responsibility of the investigator to apply the appropriate level of Urgent Safety Measure (USM) for the safety and protection of each participant in this study in order to prevent harm. USMs may be applied without prior approval from the sponsor, Competent Authority (CA) or Ethics Committee but must be reported to the sponsor immediately who will then inform the CA and EC according to local regulation. Please have full details including the action taken.

8.6 Development Safety Update Reports (DSUR)

The sponsor will be responsible for the production of DSURs once a year throughout the clinical trial, or on request, and their submission to relevant Competent Authorities and Ethics Committees as required within applicable timeframes.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size

This is a pilot proof of concept study to investigate whether complex regimens taken by patients with resistance mutations can be replaced by a simple two class single pill regimen safely in terms of viral load and adverse events.

No formal sample size calculation is performed. It is anticipated that data from 150 participants is adequate to meet the trial objectives (100 in the DTG/RPV arm and 50 in the control arm). The expected success rate is 95% based on the data reported by the SWORD 1 & 2 studies. If the observed success rate is 95% in the DTG/RPV arm at week 48 and varies from 95% to 100% in the control arm, with 150 participants (100 in the DTG/RPV arm and 50 in the control arm), the lower bound of the confidence interval of the difference in the success rate between the 2 arms (DTG/RPV – control) would varied from -9.3% to -7.4% (see table below).

Success rate			95% Confidence Interval	
DTG/RPV (n=100)	Control (n=50)	Difference	lower	upper
95%	95%	0.0%	-7.4%	7.4%
95%	96%	-1.0%	-7.9%	5.9%

95%	97%	-2.0%	-8.4%	4.4%
95%	98%	-3.0%	-8.8%	2.8%
95%	99%	-4.0%	-9.1%	1.1%
95%	100%	-5.0%	-9.3%	-0.1%

In addition, we would like to show whether the observed success rate in the DTG/RPV arm is above 95%. Therefore, we estimated power for a one-sample proportion test (Binomial test) by varying the external threshold from 80% to 90% to detect the minimum effect size at which we will have 80% power to achieve the goal (see table below).

Ho (null hypothesis): p = p0 versus Ha (alternative hypothesis): p > p0

N	alpha	p	p0	delta	power
100	5%	95%	80%	15%	100%
100	5%	95%	81%	14%	99.9%
100	5%	95%	82%	13%	99.6%
100	5%	95%	83%	12%	98.9%
100	5%	95%	84%	11%	97.2%
100	5%	95%	85%	10%	93.7%
100	5%	95%	86%	9%	93.7%
100	5%	95%	87%	8%	87.2%
100	5%	95%	88%	7%	76.6%
100	5%	95%	89%	6%	61.6%
100	5%	95%	90%	5%	43.6%

We show that, with 100 individuals in the DTG/RPV arm, we will have a 95% probability to discard a combination for which efficacy is smaller than 87% and we will select with a power of 80% the strategy for which the efficacy is above or equal to 95%.

The power calculation was made using the statistical software package nQuery Advanced, using the exact test for single proportion module (Version 8.5.2.0).

9.2 Statistical analysis plan

The statistical analysis plan will be produced during the early stages of the clinical trial before the database has been locked for the first statistical analysis. This statistical analysis plan will describe the rules used for classification of the efficacy and safety data, the primary and secondary analyses and the format of the final tables, figures, and listings to be generated. The statistical analysis plan will be finalised and approved in line with applicable SOPs before any analysis is conducted.

9.2.1 Summary of baseline data and flow of patients

The final analysis will be performed at the end of trial. A flow diagram will be produced, according to CONSORT standards, to show the disposition of all randomised patients up to the end of the trial.

Baseline data will be described according to the treatment arms: age, sex, ethnicity, length of prior ARV therapy and presence of NRTI and NNRTI mutations in historical resistance samples.

9.2.2 Primary outcome analysis

The primary endpoint will be a comparison of the percentage of participants with undetectable plasma HIV RNA levels at Week 48.

Undetectable will be defined as plasma RNA levels of <50 copies/Ml. Participants with missing data at analysis time points will be considered as having lost undetectable plasma HIV-1 RNA levels. Any patient with HIV RNA levels >50 copies/Ml at analysis time points will have a repeat test (see section 6.18 for repeat testing process). If the result from the repeat test is below 50 copies/Ml, the patient will be classified as a responder. This is to prevent false positive HIV RNA results being classified as treatment failures.

The analysis will be performed using the FDA Snapshot method. The primary population for analysis will be Intent to Treat, including all randomised patients who have received at least one dose of study medication.

Participants will be categorised as follows, based on their HIV RNA results and disposition up to the end of the trial.

HIV RNA <50 copies/Ml at Week 48

HIV RNA confirmed >50 copies/Ml at Week 48 (virological failure)

Missing HIV RNA data – discontinued randomised treatment for adverse events

Missing HIV RNA data – discontinued randomised treatment for other reasons

The intention of this study is to be a comparative pilot study. All analysis details will be included in Statistical Analysis Plan.

9.2.3 Secondary outcome analysis

Primary efficacy analysis repeated with (<200 copies/ml HIV RNA) at 24, 48, 96.

The primary efficacy analysis will be repeated for the Per Protocol population, excluding participants with serious protocol violations which could interfere with the reliability of the efficacy outcome. Examples would include taking other antiretroviral treatment within the first 48 weeks of treatment, incorrect randomisation or early discontinuation from the study for reasons unconnected to efficacy or safety. This analysis will be conducted to check the reliability of the results from the primary efficacy analysis.

In addition, a "Switch Included" analysis will be conducted, to check the outcomes of participants who discontinued randomised treatment for any reason. This analysis will follow the same methods as FDA Snapshot, but will include HIV RNA data from all participants with results available at Week 48, whether they are on or off randomised treatment. There will be no formal non inferiority outcome analysis as this is a pilot study.

All analysis details will be included in Statistical Analysis Plan.

9.3 Subgroup analyses

The sample size of 150 participants is too small to allow meaningful subgroup analyses. The two analyses described above (Per Protocol and Switch Included) will assess the reliability of the results from the primary efficacy analysis.

9.4 Adjusted analysis

The primary efficacy analysis will be by multiple logistic regression. This analysis will be adjusted for two baseline categorical variables which might influence the 48-week outcome: presence of M184V mutation at baseline and CD4 count at baseline (above versus below 350 cells/Ul).

9.5 Interim analysis

An interim analysis will be performed when 120 participants reach the week 24 visit (corresponding to 80

participants in the DTG/RPV arm and 40 participants in the control arm). This will include a primary efficacy analysis for the Per Protocol population, excluding participants with serious protocol violations which could interfere with the reliability of the efficacy outcome. This analysis will be conducted to check the reliability of the results from the primary efficacy analysis and will also include the number of patients that discontinued the study due to adverse event or death, and discontinued the study for other reasons.

In the ANRS 163 ETRAL trial (Katlama et al., JAC 2019), in which 10% of participants harboured viruses with K103N mutation, the proportion of participants in success at week 24 with a dual therapy with etravirine and raltegravir was estimated at 96.4% (95%CI 92.3 to 98.7). Therefore, for this interim analysis at week 24: The expected level of efficacy is 96%, and the unacceptable level of efficacy (p0) is 87%. With alpha = 5% (unilateral) and 80% power, if we include 80 participants in the DTG/RPV arm, we will consider that the treatment is effective to be continued if there are no more than 4 failures. We test the null hypothesis Ho: p ≤87% versus the alternative hypothesis Ha: p≥96%, with an 80% chance that the lower bound of the 95% confidence interval would exclude 87% if the true success rate (p) is 96%. This gives a 5% chance of continuing if p = p0 and an 80% chance of continuing if p ≥96.

9.6 DSMB

A DSMB will be appointed to monitor this study and draw up their own charter and decide when they will meet based on the protocol. The DSMB will meet when 80% of patients have reached 24 weeks to look at efficacy and safety, DSMB may also want to meet before or after that.

Decisions on stopping the study will be based on a combined evaluation of the efficacy and safety results. Additional issues could include treatment- emergent drug resistance, serious adverse events or high rates of discontinuation for adverse events.

9.7 Subject population

The primary population for analysis will be Intent to Treat exposed, including all randomised participants who have received at least one dose of study medication. The analyses of safety will also be conducted on the Intent to Treat exposed population.

The primary efficacy analysis will be repeated for the Per Protocol population, excluding participants with serious protocol violations which could interfere with the reliability of the efficacy outcome. Examples would include taking other antiretroviral treatment within the first 48 weeks of treatment, incorrect randomisation

or early discontinuation from the study for reasons unconnected to efficacy or safety. This analysis will be conducted to check the reliability of the results from the primary efficacy analysis.

9.8 Procedure(s) to account for missing or spurious data

In the primary efficacy analysis (FDA Snapshot), participants with missing data at analysis time points will be considered as having lost undetectable plasma HIV-1 RNA levels.

The analyses of overall participants disposition will show the number of participants who did not attend each protocol-defined visit.

9.9 Other statistical considerations.

All deviations from the statistical analysis plan will be recorded during the conduct of all analyses. If there is a decision for major modifications to the statistical analysis while the clinical trial is in progress, this will be part of a protocol amendment.

9.10 Economic evaluation

There are no plans for an economic evaluation of this trial.

10 DATA HANDLING

10.1 Data collection tools and source document identification

10.1.1 Source Data

All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) maintained at site.

10.1.2 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.

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. The following should also be recorded in the study records; confirmation of written and oral consent, the subject's clinical status, date of every study visit, date study medication was started and stopped, concomitant medications, copies of all relevant reports and laboratory tests, comments on results and reference to any adverse events.

Source documents include, but are not limited to participant medical records, serious adverse events (SAE) & reportable event forms (see section 8), questionnaires, laboratory reports, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

10.1.3 Case report forms

Subject data collected during the study will be recorded in the study specific case report forms (CRFs). In order to maintain confidentiality, the subject will be identified only by subject number.

The design of CRFs will ensure that:

- adequate collection of data has been performed
- proper paper trails can be kept to demonstrate the validity of the trial (both during and after the trial)
- only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

Data required for the study will be recorded in a web-based electronic CRF (eCRF) collection tool by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the Principal Investigator before they conduct any study related tasks. A delegation of responsibility log identifying who can enter data and/or sign off a CRF will be maintained by the Principal Investigator.

The eCRF should be kept current by entering data within two weeks of collection to enable the study monitor to review the subject status throughout the course of the study.

The data will be reviewed and approved by the Investigator following subject completion.

10.2 Data handling and record keeping

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

At the end of the study, the site will be provided with copies of their CRFs before the eCRF is decommissioned, ensuring site access to their data at all times.

Data extracted from the eCRF will be kept on a secure network drive of NEAT ID with access to authorised personnel only.

Identified only by subject number, the data are pseudo-anonymised at all times and are transferred securely using the NEAT ID file share process. All transfers are fully documented.

10.3 Archiving

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

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g. for sponsor or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required.

Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- The Investigator's Site Files must be retained for 25 years from the date of the final study report. Sponsor will inform the investigator of the retention period due date at the time when the final study report (or equivalent) is issued to the site.
- The investigator must notify sponsor of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

Archiving will be authorised by the Sponsor following submission of the end of study report.

The sponsor will be responsible for archiving the TMF. The Investigators at site(s) will be responsible for retention/archiving subject records, CRF, ISF and other study documentation (as applicable) in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

Destruction of essential documents will require authorisation from the Sponsor.

The trial database will be maintained and stored in accordance with Good Clinical Practice (GCP).

11 MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be followed for this study based on the trial risk assessment. The plan will detail monitoring frequency, requirements, and processes. The purpose of monitoring is to verify the rights and wellbeing of human subjects are protected; that trial data is accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

A monitor will conduct regular site visits for the purpose of monitoring various aspects of the study. The Investigator must agree to allow the study monitor and authorised representatives of the Sponsor, to inspect all CRF and corresponding source documents, e.g. original medical records, subject records and laboratory raw data, access to the clinical supplies, dispensing and storage areas and agree to assist with their activities if requested. The Investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator's or designee's confirmation signature.

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for sponsor authorised Quality Assurance personnel and/or authorised personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with Good Clinical Practices, and Regulatory Agency guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator will be given sufficient notice to prepare for such visits, which are planned to take usually between one and three days and may be conducted at any stage during the study. The audit will involve the review of all study related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing and return, review of all study related supplies and review of source documents against the CRF to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AE which have occurred.

12 ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/ GROUPS & INDIVIDUALS

Trial Management Committees

The only trial management committee involved in the set up and management of the clinical trial will be the DSMB.

Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is to monitor the main safety and efficacy outcome measures, any analysis, and the overall conduct of the trial, with the aim of protecting the safety and interests of the trial participants. DSMB charter to be followed. DSMB will be composed of a statistician and medical experts.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethics Committee (EC) review & reports

The study will comply with the following requirements

- Before the start of the trial, approval will be sought from a EC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the regulatory authority before they can be implemented in practice at sites)
- All correspondence with the EC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted (if required) to the EC as per country requirements.
- The Chief Investigator will notify the EC of the end of the study
- If the study is ended prematurely, the Chief Investigator will notify the EC, including the reasons for the premature termination
- Within one year after the end of the study, the sponsor will submit a final report with the results, including any publications/abstracts, to the EC

13.2 Peer review

The high-quality peer review process (initiated by study sponsor) for the trial protocol will meet the following review criteria:

a) **Independent**: At least two individual experts will review the study. Reviewers are external to the investigators' host institution and not involved in the study in any way.

b) **Expert**: Reviewers have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

c) **Proportionate**: Peer review commensurate with the size and complexity of the study.

13.3 Regulatory Compliance

This study will comply with the following:

- the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained as required by local regulations
- the protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

13.4 Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK & EU regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could be classified as a serious breach.

13.5 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

13.6 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act'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 and storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

13.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The sponsor will identify and collect the following disclosure information:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

13.8 Indemnity

The sponsor will take out appropriate insurance cover for this trial.

13.9 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial or substantial amendment at any time during a trial. If the sponsor wishes to make a substantial

amendment to the CTA or the documents that supported the original application for the CTA, the sponsor will submit a valid notice of amendment to the appropriate EC, trial registries, regulatory agencies. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

13.10 Post trial care

Post study medication will not be provided following completion of the trial. Investigators are to ensure patients have access to medication for their HIV treatment following study end.

13.11 Access to the final trial dataset

The investigators will be provided reasonable access to statistical tables, figures, and relevant reports.

Sponsor will also provide the investigators with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policies.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

A whole or part of this study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Subjects wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

15 APPENDICES

Appendix 1:	Assessment Table
Appendix 2:	AIDS Clinical Trial Group (ACTG) Grading Scale
Appendix 3:	Highly Effective Methods for Avoiding Pregnancy in Females of Child Bearing Potential
Appendix 4:	The Child-Pugh Classification System
Appendix 5:	Data Processing Agreement
Appendix 6:	Amendment History

Appendix 1: Assessment table

Both treatment arms to complete all visits.	SCREENING	BASELINE (within 28 days of screening)	WEEK 4 (+/- 7 days)	WEEK 12 (+/- 7 days)	WEEK 24 (+/- 7 days)	WEEK 48 (+/- 7 days)	WEEK 52 (+/- 7 days)	WEEK 60[1] (+/- 7 Days)	WEEK 72 (+/- 7 days)	WEEK 96 (+/- 7 days)	30 Day FU (+/- 7 days) (by phone)	Early termination visit
Eligibility Criteria Assessment	X											
Informed Consent	X											
Demographic Data	X											
Medical and Social History Including • Recreational drug use • Smoking history • Alcohol intake • Concomitant diseases • Past & present medical history, including HIV- associated conditions • Antiretroviral history (including resistance history i.e. record all resistance history by major mutations in NRTI, NNRTI, PI and II regions)	X											
Alcohol intake, smoking habit and recreational drug use		X			X	X				X		X
Physical Examination (Including Height)	X											
Weight	X	X	X	X	X	X	X	X	X	X		X
Symptom Directed Physical Exam		X	X	X	X	X	X	X	X	X		X
Vital Signs Including: • Pulse • Blood pressure (after 10 minutes resting)	X	X	X	X	X	X	X	X	X	X		X

[1] Week 60 visit is an optional visit at week 60 may be performed for subjects who are on the control arm (3 months after therapeutic modification) as required per national guidelines.

Both treatment arms to complete all visits.	SCREENING	BASELINE (within 28 days of screening)	WEEK 4 (+/- 7 days)	WEEK 12 (+/- 7 days)	WEEK 24 (+/- 7 days)	WEEK 48 (+/- 7 days)	WEEK 52 (+/- 7 days)	WEEK 60[1] (+/- 7 Days)	WEEK 72 (+/- 7 days)	WEEK 96 (+/- 7 days)	30 Day FU (+/- 7 days) (by phone)	Early termination visit
Urine pregnancy test for women of child bearing potential (WOCBP) (β-HCG) only. Investigators to remind females of reproduc ive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements. As a reminder, females of reproductive potential who changed their minds and desire to be pregnant should also be withdrawn from the study.	X	X (Predose)	X	X	X	X	X	X	X	X	X	X
Pregnancy Test : Follow-up calls should be made to WOCBP		**PREGNANCY TESTS and FOLLOW-UP TELEPHONE CALLS TO BE PERFORMED EVERY 4 WEEKS**										
Urinalysis (all tests should be performed on random spot urine. If random spot testing is not possible then 24hr urine can be performed, but only if pre-agreed with sponsor in writing) Including: • Protein:Creatinine Ratio (PCR)[2] • Albumin:Creatinine Ratio (ACR)[3] • urinary creatinine • urinary phosphate • urinary glucose (Can be performed quantitatively or by dipstick; optional if pre-agreed with sponsor in writing) • beta-2 microglobulin (optional if pre-agreed with sponsor in writing)	X	X			X	X				X		
ECG	X											
CD4 & CD8 (count / % and ratio)	X	X			X	X			X	X		X
HBV/HCV (HBV antigen test (including HbsAG, anti-HBc and HBsAb) and HCV antibodies test (if test positive for HCV antibodies, test for HCV	X					X						

[2] Random spot protein value will also be requested. 24hr urinary protein should be performed if PCR is not available, if pre-agreed with sponsor in writing (optional if pre agreed with sponsor in writing)

[3] Random spot albumin value will also be requested. 24hr urinary albumin should be performed if ACR is not available, if pre-agreed with sponsor in writing (optional if pre-agreed with sponsor in writing)

Both treatment arms to complete all visits.	SCREENING	BASELINE (within 28 days of screening)	WEEK 4 (+/- 7 days)	WEEK 12 (+/- 7 days)	WEEK 24 (+/- 7 days)	WEEK 48 (+/- 7 days)	WEEK 52 (+/- 7 days)	WEEK 60[1] (+/- 7 Days)	WEEK 72 (+/- 7 days)	WEEK 96 (+/- 7 days)	30 Day FU (+/- 7 days) (by phone)	Early termination visit
RNA, if positive and chronic for either HBV or HCV, add AST test to the biochemistry panel at screening visit. Also include Hep B surface antibodies post vax levels)												
Haematology Including: • Platelet count • RBC Count (indices MCV & MCH) • WBC count (absolute) • Haemoglobin • Hamatocrit RBC Count indices: • MCV • MCH Automated WBC differentials: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	x	x	x	x	x	x	x	x	x	x		x
Clinical chemistry (Fasted for at least 10 hours except for screening) Including: • Urea • Chloride • Alkaline phosphatise • Creatine phosphokinase • Creatinine • Calcium • Phosphate • Glucose (optional in urine if agreed with sponsor in writing) • Total bilirubin • Potassium	x*	x*	x	x	x*	x*	x	x	x	x*		x

Both treatment arms to complete all visits.	SCREENING	BASELINE (within 28 days of screening)	WEEK 4 (+/- 7 days)	WEEK 12 (+/- 7 days)	WEEK 24 (+/- 7 days)	WEEK 48 (+/- 7 days)	WEEK 52 (+/- 7 days)	WEEK 60[1] (+/- 7 Days)	WEEK 72 (+/- 7 days)	WEEK 96 (+/- 7 days)	30 Day FU (+/- 7 days) (by phone)	Early termination visit
• HsCRP (optional if agreed with sponsor in writing) • Total protein • Sodium • ALT • Albumin • Creatinine clearance (Calculations: Cockcroft-Gault (requires weight), MDRD, CK-Epi) *(* including urinary chemistry)*												
Fasting Lipids (Fasted for at least 10 hours except at screening) Including: • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides	X	X	X	X	X	X	X	X	X	X		X
HIV RNA viral load (In event of viral load failure follow section 6.18 for viral failure, resistance assessment & pharmacokinetic assessment procedures)	X	X	X	X	X	X	X	X	X	X		X
Pre-dose Pharmacokinetic assessment (A post-dose sample will be taken at early termination visit and/or in the event of virological failure (see section 6.18) within 20-28 hours of last dose)			X (Experimental arm only)			X (Experimental arm only)	X (Deferred arm only)			X (Both arms)		X
Blood sampling for PBMC isolation (Required unless exemption documented in site contract i.e. if site does not have capacity to process PBMC samples)		X				X				X		X
Quality of Life Questionnaire		X			X	X				X		X

Both treatment arms to complete all visits.	SCREENING	BASELINE (within 28 days of screening)	WEEK 4 (+/- 7 days)	WEEK 12 (+/- 7 days)	WEEK 24 (+/- 7 days)	WEEK 48 (+/- 7 days)	WEEK 52 (+/- 7 days)	WEEK 60[1] (+/- 7 Days)	WEEK 72 (+/- 7 days)	WEEK 96 (+/- 7 days)	30 Day FU (+/- 7 days) (by phone)	Early termination visit
Patient Treatment Satisfaction Questionnaire		X			X	X				X		X
Pittsburgh Sleep Questionnaire		X			X	X				X		X
DDI Assessment		X			X	X				X		X
Adherence Assessment (Self report at visit) (including date and time of last dose on PK days. Including ETV visit and/or in the event of virological failure)		X	X	X	X	X	X	X	X	X		X
AE Assessment		X	X	X	X	X	X	X	X	X	X	X
Con Med Check	X	X	X	X	X	X	X	X	X	X		X
Drug Dispensing (As per pharmacy manual)		X (Experimental arm only)	X (Experimental arm only)	X (Experimental arm only)	X (Experimental arm only)	X	X	X	X			

Appendix 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

Appendix 3: Highly Effective Methods for Avoiding Pregnancy in Females of Child Bearing Potential

The following is the all inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to Females of Child Bearing Potential (FCBP) with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant

2. Intrauterine device or intrauterine system

3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])

4. Injectable progestogen [Hatcher, 2011]

5. Contraceptive vaginal ring [Hatcher, 2011]

6. Percutaneous contraceptive patches [Hatcher, 2011]

7. Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

References

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3 2.

Appendix 4: The Child-Pugh classification system

The Child-Pugh classification is a scoring system used to determine the prognosis with cirrhosis. Scoring is based upon several factors: albumin, ascites, total bilirubin, prothrombin time, and encephalopathy, as follows:

	Score: 1 point	**Score: 2 points**	**Score: 3 points**
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 - 6
- **Class B** is score 7 - 9
- **Class C** is score >9

Patients with a score of 10 or more (in the Class C category) have a prognosis with 1-year survival being about 50%. Patients with Class A or B have a better prognosis of 5-years, with a survival rate of 70%- 80%.

Appendix 5: Data Processing Agreement

Definitions:

- "Protocol" means the document entitled "The effect of switching to Dolutegravir and Rilpivirine combination therapy in patients with HIV-1 and the K103N mutation" containing the details of the study as developed by the Lead Sponsor and approved by the relevant Ethics Committee(s).
- "Sponsor" means "NEAT ID"
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Lead Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").

- "Applicable Law" means any applicable data protection or privacy laws, including:

a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");

b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;

- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymised information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organisation, unless the Data Processor is required to do so according to Union or Member State law.

2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.

3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.

4. The Data Processor shall implement appropriate technical and organisational measures to prevent that the Personal Data processed is:

(i) accidentally or unlawfully destroyed, lost or altered,

(ii) disclosed or made available without authorization, or

(iii) otherwise processed in violation of Applicable Law.

5. The appropriate technical and organisational security measures must be determined with due regard for:

(i) the current state of the art,

(ii) the cost of their implementation, and

(iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organisational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)

7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organisational security measures have been implemented.

8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organisational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.

9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

10. The Data Processor must without undue delay in writing notify the Data Controller about:

(i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,

(ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, Personal Data stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or

(iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.

11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:

(i) the nature of the Personal Data breach, stating the categories and (by approximation) the number

of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);

(ii) the likely consequences of the Personal Data breach;

(iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.

12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).

13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organisational measures for the fulfilment of the Data Controller's obligation to respond to such requests.

14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.

16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organisational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA

Appendix 6: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.0 to 2.0	23 March 2018	Emily Hutton. Project Manager	Formatting and minor edit to text to ensure consistency. Version 1.0 not submitted & not approved.
2	2.0 to 3.0	11 July 2018	Barbara Gastl, Project Director	1. St Stephens Clinical Research removed as study sponsor and responsible party for Project Management & Biometrics and Data Management. 2. Introduction of NEAT ID as the sole sponsor for the trial and ROKC as CRO for Project Management, Data Management and Statistics. 3. Inclusion criteria No. 3 updated in line with UK REC comments as follows "Is capable of giving informed consent~~, or if appropriate, subjects having an acceptable individual capable of giving consent on the subject's behalf.".~~ 4. Additional risk/safety information added to address emerging NTD safety information. Pregnancy testing also added to all visits from baseline to ETV. 5. Clarification to Reference Safety Information, cautioning on the use of concomitant medicines that inhibit CYP3A and effects to exposure of rilpivirine. 6. Addition of pregnancy tests for WOCBP at every study visit and home testing every 4 weeks throughout the trial 7. Clarification of applicable Reference Safety Information in section 8.1
3	3.0 to 4.0	01Jul2020	Zainib Shabir, Project Manager	1. Align all protocols for all territories following initial approval 2. Updated RSI information to SmPC of Juluca in-line with previously submitted amendments 3. Correct minor admin errors and minor inconsistencies 4. Addition of interim analysis at week 24 5. Updated exclusion criteria 14 and 15 to include an exemption based on local practice for vaccination of patients at low-risk of acquiring Hepatitis B 6. Updated exclusion criteria 25 to include an exemption for hyperbilirubinaemia due to atazanavir exposure 7. Removed the requirement for the screening pregnancy test to be performed in serum to

				allow for different standard practices at sites 8. Addition of Week 52 PK sampling for deferred switch patients to match the Week 4 PK sampling for immediate switch patients 9. Replaced Appendix 2 AE grading table with an external link to the most up-to-date version 10. Added a Data Processing Agreement as Appendix 5
4	4.0 to 5.0	30Oct2020	Jacob Lowman, Project Manager	1. Expanded section 9 on statistical analysis with more information concerning the analysis and powering of the study, including the addition of a Week 24 interim analysis 2. Corrected conditions of virological failure to correctly state repeat test should be at least 14 days from initial detectable test 3. Correction of primary outcome measure b. to be investigated over 48 weeks rather than 96 weeks 4. Updated risk wording concerning pregnancy in women taking dolutegravir as provided by the IMP manufacturer 5. Removed incorrect mentions of Trial Steering Committee and Trial Management Group in various section 6. Numerous minor administrative changes

~This page is to be left blank~