Bictegravir/emtricitabine/tenofovir alafenamide plus doravirine in highly treatment-experienced men with multidrug-resistant HIV

NCT04538040
2023

Protocol Title:	An open label study evaluating the safety and efficacy of switching from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine, in male HIV+ subjects ≥ 45 years with multi-drug resistant virus and virologic suppression (documented with at least one viral load result ≤ 50 copies per mL) during the last 6 months on current therapy.
Switch Therapy:	Bictegravir/emtricitabine/tenofovir alafenide plus doravirine:
Investigator:	F. Lisa Sterman MD, MPH
Phase:	IV
Protocol Number:	BETD-001
Version No.:	3.0
Date:	06-25-2021

PROTOCOL APPROVAL – SPONSOR SIGNATURE PAGE

This study protocol entitled:

An open label study evaluating the safety and efficacy of switching from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine, in male HIV+ subjects ≥ 45 years with multi-drug resistant virus and HIV virologic suppression (documented with at least one viral load result ≤ 50 copies per mL) during the last 6 months on current therapy.

The information this protocol contains is consistent with the current risk/benefit evaluation of the study drug as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP).

This protocol is approved by:

Name: _____

Signature: _____

Date: _____/_____/_____(DD/MMM/YYYY)

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1.0 GLOSSARY

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the plasma concentration curve from time 0 to infinity
AUC_{last}	Area under the plasma concentration curve from time 0 to the last observable concentration
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve, from time 0 to the last measurable concentration
BLQ	Below the limit of quantification
BIC/FTC/TAF + DOR	Bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine
bpm	Beats per minute
BUN	Blood urea nitrogen
CK	Creatine kinase
CL	Total clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
CV	Coefficient of variation
EOT	End-of-treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practices
h	Hour
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IRB	Institutional review board
k_{el}	First-order rate constant for elimination of drug

LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
RBC	Red blood cell (count)
RNA	Ribonucleic Acid
RPV/FTC/TAF + DTG	Rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
t_{lag}	Time between drug administration and first observed concentration above lower limit if quantitation in plasma
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
WBC	White blood cell (count)
WHO	World Health Organization

2.0 PROTOCOL SYNOPSIS

Title	An open label study evaluating the safety and efficacy of switching from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine, in male HIV+ subjects ≥ 45 years with multi-drug resistant virus and virologic suppression (documented with at least one viral load result ≤ 50 copies per mL) during the last 6 months on current therapy.
Protocol Number	BETD-001
Switch therapy	Bictegravir/emtricitabine/tenofovir alafenide plus doravirine
Number of Sites and Countries	One site, US
Phase	Phase IV
Indication	Male HIV+ subjects over 45 years old with prior multidrug resistance to HIV therapy, with a prior positive response to rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, and switching to bictegravir/emtricitabine/ tenofovir alafenamide in combination with doravirine.
Study Design	The current study proposal is an open label observational trial for maintenance of virologic suppression, and is designed as a non-inferiority switch trial. The study will involve approximately 30 patients, which includes a PK arm of approximately 10 patients. The study will also include secondary outcomes of quality of life (QOL) and weight changes Hypothesis: Patients with prior NUC or NNRTI resistance (but not to rilpivirine *or* doravirine) will maintain their virologic suppression after a drug regimen switch from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine. The switch therapy will avoid food interactions, and will be well tolerated by subjects.
Primary Endpoint	1. Percentage of patients with viral HIV load (VL) <50 and <200 copies/mL at 48 weeks
Secondary Endpoints	1. Tolerability 2. Changes in body mass index (BMI) from baseline to 48 weeks

	3. Provide data on heavily treatment experienced (HTE) patients, switching to a bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine containing-regimen. 4. Confirm absence of drug/drug interactions between bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine based on 24-hour PK at week 4 (+/- 14 days) with time points at predose (-0.5 hr), 0.5, 1, 2, 4, 6, 8, 12, and 24 hours for a subset of 10 subjects. 5. Assess AE's of any grade and relationship to the drug combination occurring in at least 5% of participants or more. 6. Improvement in well-being and sleep inventory as measured by The Pittsburgh Sleep Quality Index (PSQI) & The Work Productivity and Activity Impairment Questionnaire (WPAI).
Study Duration	1. Duration of enrolment period: 12 months 2. Subjects entering treatment per month: 10 patients 3. First subject in to 50% enrolment: 3 months 4. 50% enrolment to last subject in: 6 months (100% at 6 months)
Number of Subjects	30 (10 PK subjects as a subset)
Subject Population	Male HIV+ subjects over 45 years old with stable effective antiviral response (HIV RNA copies less than 50/mL on at least one occasion in the six months prior to switching therapy) with rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir switching to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine
Inclusion Criteria	1. HIV positive Males, age 45 or older 2. Any genotypic or phenotypic resistance except k65R, 69 insertion, integrase resistance, or resistance to rilpivarine or doravirine. 3. Receiving combination antiretroviral regimen of rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir > 12 months and with viral load $\leq$50 copies/ mL on at least one occasion within the six months prior to switch. 4. Suppressed viral load as defined by one plasma HIV RNA level $\leq$ 50 copies/mL within previous 6 months. 5. Capable of providing informed consent
Exclusion Criteria	1. Any current or prior integrase inhibitor resistance

	2. Nucleoside reverse transcriptase (NRTI) mutation 69 insertion or k65R mutation 3. Documented second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (rilpivirine or doravirine)
Statistical Methods	In this study, subjects will have stable prior antiretroviral therapy (HIV RNA copies <50/mL on at least one occasion in the 6 months prior to the study), and the aim is to determine if the protocol therapy will continue to suppress HIV activity. The goal is to determine the number of subjects who have 1) less than 50 copies/mL and 2) less than 200 copies/mL HIV at week 48. The secondary objective of the study is to determine the quality of life and weight stabilization provided by the switch therapy as measured by the Pittsburgh Sleep Quality Index (PSQI), The Work Productivity and Activity Impairment Questionnaire (WPAI) and BMI assessment. Values will be compared at baseline and at 48 weeks.

3.0 BACKGROUND INFORMATION

3.1 Study Rationale

In recent years with the advent of high barrier integrase strand transfer inhibitors (INSTI) and the aging HIV/AIDS population, providers have initiated proactive anti-retroviral (ARV) switches away from protease inhibitors, for minimization of coronary artery disease (CAD) risk associated with protease inhibition (1). Many legacy HIV patients have 2 and 3 class resistant viruses. Common regimens that were used for switch to overcome resistant virus and maintain un-detectability off protease regimens included a switch to rilpivirine, emtricitabine, tenofovir alafenamide plus dolutegravir. With the approval of bictegravir/emtricitabine/tenofovir alafenamide and doravirine, both very high genetic barrier antivirals, and with this regimen being two single small daily tablets, both with the advantage of elimination of need for food requirement in an antiviral regimen and fewer drug/drug/interactions (DDI), switching from rilpivirine/emtricitabine/tenofovir alafenamide plus dolutegravir to bictegravir/ emtricitabine/ tenofovir alafenamide plus doravirine is a very attractive current option. There are no theoretical pharmacokinetic (PK) interactions between these medications, but there exists a data gap as they have not been studied in combination for safety and efficacy. The current study proposal is an open label observational trial for maintenance of virologic suppression, and is designed as a non-inferiority switch trial. The study will involve approximately 30 patients, which includes a PK arm of approximately 10 patients. Given known incidence of adverse events with dolutegravir, including CNS toxicities(9), it might be expected that the switch regimen will have an improved adverse event profile. There is increasing evidence of weight gain challenges with integrase inhibitor class (including dolutegravir) containing regimens, but bictegravir containing regimens appear to offer equivalent weight gain compared with dolutegravir(10). The study will also include secondary outcomes of quality of life (QOL) as measured by the Pittsburgh Sleep Quality Index (PSQI) and The Work Productivity and Activity Impairment Questionnaire (WPAI), and subject weight as measured by Body Mass Index at baseline and 48 weeks.

3.2 Anticipated Risks and Safety concerns for the switch

There are known risks associated with bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine (see data information for the combination in the product prescribing information in Appendices 4 and 5).

It is not anticipated that the switch will place subjects at greater risk than their current therapy.

If subjects participate in the PK evaluation, there are minor risks associated with blood sampling.

4.0 STUDY OBJECTIVES

Primary objectives:

1. Percentage of patients with viral HIV load (VL) <50 and <200 copies/mL at 48 weeks

Secondary objectives:

1. Tolerability
2. Changes in body mass index (BMI) from baseline to 48 weeks
3. Provide safety and pharmacokinetic data on subjects switching to a bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine regimen.
4. Confirm absence of drug/drug interaction between bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine based on 24 hour PK at week 4 (+/- 14 days) with time points at predose (-0.5 hr), 0.5, 1, 2, 4, 6, 8, 12, and 24 hours for n=10.
5. Improvement in well-being and sleep inventory as measured by the Pittsburgh Sleep Quality Index (PSQI) and The Work Productivity and Activity Impairment Questionnaire (WPAI).

5.0 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

The current study proposal is an open label observational trial for maintenance of virologic suppression, and is designed as a non-inferiority switch trial. The study will involve approximately 30 patients, which includes a PK arm of approximately 10 patients. The study will also include secondary outcomes of quality of life (QOL) as measured by the Pittsburgh Sleep Quality Index (PSQI) and The Work Productivity and Activity Impairment Questionnaire (WPAI), and weight changes measured by body mass index (BMI) over the 48 week study period.

Hypothesis:
HIV+ male patients 45 years and older with prior NUC or NNRTI resistance (but not to rilpivirine or doravirine) will maintain their virologic suppression after a drug regimen switch from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir to bictegravir/emtricitabine/tenofovir alafenamide

in combination with doravirine. Subjects will maintain weight, and will tolerate the switch therapy. Subject's quality of life will be maintained or improved.

5.2 Duration of Study Participation

For each Subject, the study duration will span from the date of signed, written informed consent through the end of treatment (EOT) visit, expected to be about 48 weeks with the option of returning for additional unscheduled visits if retests are required.

Subjects who have signed the informed consent form and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the Investigator is to maintain a screening log that documents the Subject initials and reason(s) for screen failure. A copy of the log should be retained in the Investigator's study files. Instructions on how to handle Subject screening, screen failure, and recruitment will be provided in a dedicated document.

5.2.1 Study Procedures

The procedures to be performed at each study visit are outlined below.

5.2.2 Screening/Baseline

The following activities will be performed at baseline:

- Informed consent (prior to any study-specific procedures).
- Study inclusion/exclusion criteria.
- Collect year of HIV diagnosis
- Demographic information (age, gender, race, ethnicity, as allowed by local regulation).
- Height and weight, body mass index (BMI).
- Pittsburgh Sleep Quality Index (PSQI)
- The Work Productivity and Activity Impairment Questionnaire (WPAI)
- HIV viral load
- CD4 count within 3 months of study entry
- Physical examination
- Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology: complete blood cell count (CBC)
- Serum chemistry
- Urinalysis
- Adverse events reported after the Subject provides informed

consent.

- Treatment switch initiated

5.2.3 28 Days (+/- 14 days)

- Pharmacokinetic sampling (subset of 10 subjects)
- Physical examination
- Weight & Body Mass Index (BMI)
- Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology for CBC assessment
- HIV viral load
- Serum chemistry
- Urinalysis
- Adverse event updates.

5.2.4 Week 12 (+/- 14 days)

- Physical examination
- Weight & Body Mass Index (BMI)
- Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology: for CBC assessment
- HIV viral load
- Serum chemistry
- Urinalysis
- Adverse event updates.

5.2.5 Week 24 (+/- 14 days)

- Physical examination
- Weight & Body Mass Index (BMI)
- Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology: for CBC assessment
- HIV viral load
- Serum chemistry
- Urinalysis
- Adverse event updates.

5.2.6 Week 36 (+/- 14 days)

- Physical examination
- Weight & Body Mass Index (BMI)Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology: for CBC assessment 16aematocrit16aematocrit
- HIV viral load
- Serum chemistry:
- Adverse event updates.

5.2.7 Week 48/End-of-treatment (EOT)/Early Termination Visit (+/- 14 days)

The following procedures will be performed at the EOT visit:

- Weight & Body Mass Index (BMI)
- Pittsburgh Sleep Quality Index (PSQI)
- The Work Productivity and Activity Impairment Questionnaire (WPAI).
- Physical examination
- Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Hematology: for CBC assessment
- HIV viral load
- CD4 count
- Serum chemistry:
- Urinalysis
- Adverse event updates.

5.3 Randomisation and Blinding

Not applicable.

5.4 Source Data

Source documents (including all demographic and medical information, CRFs, and a copy of the signed informed consent form [ICF] indicating the study number and title) for each Subject in the study will be maintained by the Investigator (generally in the Subject's files), and all information in the CRFs must be traceable to the source documents.

All data should be recorded directly into the Subject's medical record as source data. It will be confirmed at an initiation visit which documents will be considered

as source data for the site. These will be documented and reviewed by the monitor at each monitoring visit.

Source documents must be available to document the participation of the Subject and substantiate the integrity of study data collected.

6.0 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Subject Inclusion Criteria

Each Subject (male) **must meet all** of the following criteria to be enrolled in this study:

1. HIV positive Males, age 45 or older
2. Any genotypic or phenotypic resistance except k65R, 69 insertion, integrase resistance, or resistance to rilpivarine or doravirine.
3. Receiving combination antiretroviral regimen of rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir > 12 months and with viral load $\leq$50 copies/ mL on at least one occasion within the previous 6 months.
4. Suppressed viral load as defined by one or more plasma HIV RNA levels $\leq$ 50 copies/mL within previous 6 months.
5. Capable of providing informed consent.

6.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Any current or prior integrase inhibitor resistance
2. Nucleoside reverse transcriptase (NRTI) mutation 69 insertion or k65 mutation
3. Documented second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (rilpivirine or doravirine)

7.0 SUBJECT WITHDRAWAL CRITERIA

7.1 Removal of Subjects from Assessment

A Subject may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Subject voluntarily discontinues participation in the study (consent withdrawal)
- Toxicity-related criteria
- Any clinically relevant signs or symptoms that, in the opinion of the Investigator, warrant Subject withdrawal.
- Protocol deviation (including non-compliance).
- Disease progression or relapse
- Lost to follow-up
- The Investigator determines it is in the best interest of the Subject to discontinue the Subject's participation in the study

The Investigator will also withdraw a Subject if the Investigator terminates the study. If a Subject is discontinued because of an AE, the event will be followed until it is resolved, resolved with sequelae, not recovered (death due to another cause), or death (due to an SAE).

Reasonable effort should be made to contact any Subject lost to follow-up during the course of the study in order to complete assessments.

7.2 Handling of Withdrawals

Subjects who discontinue study drug or active participation in the study will no longer receive study drugs. When a Subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the case report form (CRF). Whenever possible, all Subjects who discontinue study drug will undergo all the assessments at the EOT visit. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Following a minimum of two documented unsuccessful telephone calls, a registered letter will be sent to the Subject in a final attempt to ensure protocol compliance.

It is vital to obtain follow-up data on any Subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures.

7.3 Termination of Study

The Investigator can terminate the study at any time for significant deviations from the protocol or due to difficulties experienced in running the study.

The Investigator may terminate this study for any of the following reasons:

- Non-compliance with protocol, GCP, and/or regulatory requirements
- Observation of unexpected, significant, or unacceptable risk to Subjects.
- An adequate number of Subjects cannot be recruited
- False documentation in the CRF
- Other administrative reasons.

Should the study be discontinued prematurely, all study materials must be returned to the Investigator or Investigator's designee.

7.3.1 Regular Termination of Study

The end of this study is defined as the date of the last visit of the last Subject participating in the study. Within 90 days of the end of the study, the Investigator will notify the institutional review board/independent ethics committee (IRB/IEC) and the relevant regulatory authorities about the regular termination of the study as required according to national laws and regulations. If the study has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

7.3.2 Premature Termination of Study

The study may be terminated prematurely for any reason and at any time by the Investigator, IRB/IEC or regulatory authorities. The IRB/IEC and the relevant regulatory authorities will be informed about reason and time of termination according to the applicable laws and regulations.

8.0 TREATMENT OF SUBJECTS

8.1 Treatments Administered

Orally administered (single doses daily) bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine at physician prescribed doses.

50 mg of bictegravir (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate) as a single tablet daily.

Doravirine 100mg tablet daily.

8.2 Assessment of Compliance and procedures

Investigator or designee will record time of administration of study drugs in the CRF on the day prior to PK sampling, the day of PK sampling, and the day after PK sampling for subjects participating in the PK portion of the study. Study drug should be taken in the morning on the day prior to PK sampling, the day of PK sampling, and after the 24 hour PK draw on the day after PK sampling.

9.0 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

9.1 Pharmacokinetic Analyses

Full PK assessments will be taken pre-dose (-0.5 hr), and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing on day 28 (+/- 14 days). Subjects may be asked to return for an unscheduled visit to test/retest PK samples if the initial data is found to be invalid

The PK parameters to be calculated will include, but are not limited to, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, k_{el}, t_{max}, t_{lag}, CL, Vd and $t_{½}$. The PK parameters and concentrations will be summarised by dose levels among the PK evaluable Subjects. Plots of mean plasma concentration of bictegravir and doravirine over time will be provided.

10.0 ASSESSMENT OF SAFETY

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol.

Follow-Up for Toxicities
Subjects whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4 week intervals, until resolution or stabilisation of the event, whichever comes first. All Subjects must be followed up for AEs and SAEs for 30 days following the last dose of study therapy.

10.1 Safety Parameters

10.1.1 Adverse Events

Adverse events are continuously monitored beginning at enrolment (date of signed informed consent) and up to 30 days after the last dose of the study drug. Adverse events will be graded using CTCAE version 5.0

10.1.2 Adverse Event Definition

An AE is any untoward medical occurrence in a Subject or clinical investigation. Subject will have been administered a pharmaceutical

product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

10.1.3 Laboratory investigations criteria for AE

Any abnormal laboratory results (hematology, clinical chemistry, or urinalysis) or other safety parameters (e.g., radiological scans, ECGs, and vital sign measurements, etc), felt to be clinically significant in the medical and scientific judgement of the Investigator are considered AEs. Examples of criteria for determining whether an abnormal finding is clinically significant and should be reported as an AE are:

- CTCAE Grade 4
- Laboratory result is associated with accompanying symptoms or signs
- Laboratory result requires additional diagnostic testing or medical/surgical intervention
- Laboratory result leads to a change in study dosing or discontinuation from the study significant additional concomitant drug treatment, or other therapy
- Laboratory results worsen from baseline
- Laboratory result is considered to be an AE by the Investigator or Sponsor.

However, merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE. Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Subject population and Subject's individual condition, are not to be reported as AEs.

Laboratory and other safety assessments can be considered SAEs when criteria apply

Relationship of Adverse Events

Not related: An AE for which there is no reasonable temporal association between its onset and administration of

the investigational drug, or that can reasonably be explained by other factors, including underlying disease, complications, concomitant drugs or concurrent treatment.

Note: Even if the Investigator feels there was no relationship to study medication, the AE experience is to be reported.

Unlikely to be related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possibly related: An AE for which there is a reasonable temporal association between its onset and administration of the investigational drug (including the course of treatment after withdrawal of the drug), for which other causal factors may not be excluded.

Probably related: An AE for which there is a reasonable temporal association between its onset and the administration of the investigational drug, including the course after treatment withdrawal, and which is more likely to be explained by the test drug than by any other cause (e.g., underlying disease, complications, concomitant drugs or concurrent treatment).

Definitely related: An AE that is judged as undeniably related to the administration of study medication. Factors taken into consideration when a definite relationship is assigned include whether the AE:

- Followed a clear temporal sequence from administration of study medication.
- Could not be possibly explained by the known characteristics of the Subject's clinical state, environmental or toxic factors, other modes of therapy administered to the Subject.
- Disappeared or decreased on cessation or reduction in dose of study medication.
- Reappeared or worsened when study medication was re-administered.

- Followed a response pattern known to be associated with administration of study medication.

10.1.4 Intensity of Adverse Events

For grading the intensity of an AE, the following CTCAE categories will be applied:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

10.1.5 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent adverse event (TEAE) if first onset or worsening is after first intake of study drugs.

10.1.6 Serious Adverse Events

An SAE is an AE that suggests a significant hazard, contraindication, side-effect, or precaution. With respect to human clinical experience, this includes any event that:

- Results in death.
- Is life-threatening.*
- Requires in-Subject hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other medically important condition.

* Life-threatening in the definition of a SAE or adverse reaction refers to an event in which the Subject *was at risk of death at the time of event*; it does not refer to an event that hypothetically might have caused death if it were more severe.

All of the above criteria apply to the case as a whole and should not be confused with the outcomes of individual reactions/events. More than one of the above criteria can be applicable to the one event.

10.1.7 AE or SAE Exceptions

The following events must not be reported as AEs or SAEs:

- Admissions to the hospital, not associated with deterioration in condition, for the following:
  - supportive therapy, e.g., respite care,
  - standard procedures, e.g., pre-planned treatments,
  - elective procedures, e.g., a previously scheduled surgical procedure,
  - disease-related investigations, e.g., pre-planned laboratory or instrumental assessments.

10.1.8 Laboratory Evaluation

10.1.8.1 Safety Laboratory Parameters

The following safety laboratory tests will be performed:

Hematology (peripheral blood)

Serum chemistry (peripheral blood):

Urine Testing

10.1.9 Other Safety Parameters

10.1.9.1 Vital Signs

Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature will be recorded throughout the study as noted in Section 5.2.1 and Appendix 1.

10.1.9.2 Physical Examination

Physical examinations will be performed as noted in Section 5.2.1 and Appendix 1. The physical examination will consist of the following: evaluation of the general appearance, head, eyes, ears, nose, throat,

lymph nodes, heart/cardiovascular, respiratory, abdomen, genitourinary, musculoskeletal/extremities, neurological status, and dermatology.

Body weight (with BMI) and height will be measured at as noted in Section 5.2.1 and Appendix 1.

10.2 Recording and Reporting Adverse Event/Intercurrent Illnesses

It is the responsibility of the Investigator to document all AEs that occur during the study. All AEs observed during the study from the time the Subject signs the ICF through 30 days after the last dose of the study drug on the AE page of the CRF. Information to be collected includes: event term, date of onset , pattern of AE (intermittent or continuous), outcome of the event, Investigator-specified assessments of severity, seriousness, relationship to study drug, date of resolution of the event, any required treatment or evaluations, and whether the event caused study discontinuation.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported.

Adverse events will be elicited by asking the Subject a non-leading question, for example “Have you experienced or are you experiencing any new or changed symptoms since we last asked/since your last visit?” Adverse events should be reported on the appropriate page of the CRF.

10.3 Adverse Event Follow-up Procedures

All AEs must be followed-up until the event has resolved or stabilised or the relationship to study medication is clarified.

11.0 STATISTICAL METHODS

11.1 General Methods

A SAP will be prepared as a separate document that will include a detailed description of statistical analyses and summarisation procedures (including templates for tables, listings, and figures). The SAP will be finalised before initiating any statistical analysis.

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise, and will be performed using SAS® Version 9.2 or higher. All

summaries, listings, figures, and analyses will be performed by dose level/schedule (as applicable).

Data will be summarised using descriptive statistics (number of Subjects, mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

Plasma concentration data at each time point will be summarised with number of Subjects, mean, median, minimum, maximum, SD, and coefficient of variation (CV; %) for each dose level/schedule (as applicable). All PK parameters will be summarised with number of Subjects, mean, standard deviation, median, minimum, maximum, geometric mean, CV (%), and log-transformed SD.

All data will be provided in by-Subject listings.

11.2 Demographics and baseline characteristics

Demographic and baseline disease characteristic data will be summarised by dose.

11.3 Analysis of Primary endpoints

11.3.1 Safety and Tolerability

The safety of the therapies will be assessed by monitoring incidence of AEs, clinical laboratory tests, vital signs, and physical examination. Safety will be monitored throughout the study for all Subjects. Safety data will be summarised by dose level/schedule (as applicable). Safety summaries will contain only data collected during on-treatment period, unless specified otherwise.

11.3.1.1 Adverse Events

The verbatim terms used in the CRF by the Investigator to identify AEs will be coded by system organ class and preferred terms using MedDRA (current version). All reported TEAEs will be included in the analysis.

AEs will be summarised by system organ class and preferred term.

The following summaries will be produced:

- All TEAEs
- Treatment related TEAEs

- Grade 3 or higher TEAEs
- Most commonly reported TEAEs (i.e., those events reported by ≥ 5% of all Subjects)
- SAEs
- Discontinuations due to AEs.

By-Subject listings will be provided for all AEs, SAEs, AEs leading to discontinuation of treatment, and deaths.

11.3.1.2 Clinical Laboratory Tests

Safety laboratory data (hematology, serum chemistry and urinalysis) will be summarised for each laboratory parameter.

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots may be specified in the SAP.

11.3.1.3 Vital Signs

The vital signs parameters that will be summarised are pulse, blood pressure (systolic and diastolic), respiratory rate, and body temperature.

Descriptive statistics for the actual values and changes from baseline in vital signs data for each dose level over time will be summarised.

11.3.1.4 Physical Examination

A data listing of Subjects with abnormal physical examination results will be provided.

11.3.1.5 Tolerability

Tolerability of study drugs will be assessed by summarising the number of AE/SAE occurring during the study.

11.3.1.6 Pharmacokinetic Analyses

Individual Subject plasma concentration-time data of bictegravir and doravirine will be determined as listed in the protocol.
The PK parameters to be calculated will include, but are not limited to, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, kel, t_{max}, t_{lag}, CL, Vd and $t_{½}$. The PK parameters and concentrations will be summarised by dose levels among the PK evaluable

Subjects. Plots of individual and mean plasma concentration of over time, data summaries, and data listings will be provided for the PK analysis set.

The SAP will provide details of the analysis and presentation of the results.

11.3.2 Safety and Tolerability

Safety and tolerability of the new dosing regimen will be assessed by evaluation of the AE/SAE events occurring after the switch.

11.3.3 Pharmacokinetics Analyses

Individual Subject plasma concentration-time data of bictegravir and doravirine will be analysed using non-compartmental model (WinNonlin®).

In the 10 subject sub-cohort, the plasma samples of bictegravir and doravirine for PK assessments will be taken prior to dosing (-0.5 hr), and at0.5, 1, 2, 4, 6, 8, 12, and 24 hours on day 28 (+/- 14 days). Subjects may be asked to return for an unscheduled visit to test/retest PK samples if the initial data is found to be invalid. All calculations will be based on actual sampling times.

The PK parameters to be calculated will include, but are not limited to, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, kel, t_{max}, t_{lag}, CL, Vd and $t_{½}$. The PK parameters and concentrations will be summarised by dose levels among the PK evaluable Subjects. Plots of individual and mean plasma concentration of over time, data summaries, and data listings will be provided for the PAS.

The PK parameters will be Log (e) transformed prior to analysis.

The SAP will provide details of the analysis and presentation of the results.

11.3.4 Preliminary Assessment of Clinical Activity

In this study, subjects will have stable prior antiretroviral therapy (HIV RNA copies $\leq$50/mL on at least one occasion in the 6 months prior to the switch), and the aim is to determine if the protocol therapy will continue to suppress HIV activity. The goal is to determine the number of subjects who have 1) $\leq$ 50 copies/mL and 2) less than 200 copies/mL HIV at week 48.

The secondary objective of the study is to determine the quality of life and weight stabilization provided by the switch therapy.

11.4 interim analysis

No formal interim analyses are planned.

11.5 Statistical Considerations

The target sample size for the study is 30 subjects.

Number of subjects maintaining HIV suppression (either ≤50 copies/mL or <200 copies/mL) will be tabulated.

Descriptive analyses will be tabulated for subject weight and body mass index (BMI) prior to commencing therapy and at 48 weeks after dosing commences.

Quality of life analysis will be determined by comparison of baseline QOL scores (Improvement in well-being and sleep inventory as measured by The Pittsburgh Sleep Quality Index (PSQI) & The Work Productivity and Activity Impairment Questionnaire (WPAI)) with scores at 48 weeks.

11.6 Procedure For Accounting for Missing, Unused, and Spurious Data

In general, the values for missing data will not be imputed. For laboratory data the missing baseline values will be replaced by Screening value if available, otherwise it will be treated as normal for summary of graded laboratory of abnormalities. Subjects may be asked to return to the clinic to test or retest PK values if the initial results are found to be invalid.

The values will not be imputed for missing vital signs and other safety data, however, missing baseline values will be replaced by Screening values if available. Also, missing relationship between AE and study medication will be considered as related to treatment and missing severity of an AE will be summarised as severe AE, following conservative principle.

All available data for a Subject who do not complete the study will be included in the data listing.

11.7 Derived And Transformed Data

Pharmacokinetic concentration values below the limit of quantification (BLQ) will be treated as zero for the determination of summary and order statistics. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 Subject has a concentration value BLQ for the time point, then the minimum value will be

displayed as BLQ. If more than 50% of the Subjects have a concentration data value BLQ for the time point, then the minimum and median values will be displayed as BLQ. If all Subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile, median, third quartile, maximum) will be displayed as BLQ.

PK parameters selected for statistical analysis will be log transformed. Concentration values that are BLQ will be considered missing for any ratio or natural-log transformed statistical analyses.

Laboratory data that are continuous in nature, but are less than the lower limit of quantification or above the upper limit of quantification, will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

11.8 Deviations From The Original Statistical Plan

Any deviations from the original SAP as described in this protocol will be agreed to by the Investigator, documented, and justified in an amendment, the final SAP, or the final study report, as appropriate.

11.9 Subject Selection For Analyses

The following analysis sets will be evaluated and used for presentation of data:

- Dose Determining Set (DDS): All Subjects who complete at least 28 days dosing. Subjects in this set will be denoted as evaluable for safety assessment.
- Safety Analysis Set (SAS): All Subjects who are enrolled and receive at least one dose of study treatment. Subjects will be classified according to the treatment received. The SAS will be the primary set for the analysis of safety data.
- Full Analysis Set (FAS): All Subjects who are enrolled and receive at least one dose of study treatment. Subjects will be classified according to the assigned dose level and schedule. The FAS will be the primary analysis set for efficacy analysis and the default analysis set for all other analyses, unless otherwise specified.
- PK Analysis Set (PAS): All Subjects who have at least one blood sample providing evaluable PK data. The PAS will be used for PK analyses.

12.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical monitor(s) should be given direct access to primary subject data (i.e., source data) which supports the data on the CRFs for the study, i.e., general practice charts, hospital notes, appointment books, original laboratory records etc. Because this enters into the realm of subject confidentiality, this fact must be included in the ICF that the subject signs. Other authorised persons such as auditors may need to have direct access to this source data.

12.1 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

12.2 Source Documents

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, Subject files, records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

12.3 Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g., domestic and foreign regulatory authorities) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of Subject identities.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

An independent audit at the study site may take place at any time during or after the study. The independent audit can be carried by the Quality Assurance (QA) department of a regulatory authority.

13.1 Quality Control

Quality control is defined as the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

13.2.1 Inspection

An inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at any other establishments deemed appropriate by the regulatory authorities.

13.2.2 Audit

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated standard operating procedures (SOPs), GCP and the applicable regulatory requirements.

14.0 ETHICS

14.1 Ethical Conduct of the Study

This clinical study will be conducted in compliance to this protocol, and in accordance with ICH GCP, the provisions of the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, 2013), designated SOPs, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct. The IRB/IEC must be constituted according to the local laws/guidelines.

14.2 Institutional Review Board/Independent Ethics Committee Approval

Before initiating a study, the Investigator will have the written and dated approval/favorable opinion from the relevant IRB/IEC for the study protocol (and any amendments), ICF, ICF updates, Subject recruitment procedures (e.g., advertisements), and any other written information to be provided to Subjects. Approval will be indicated in writing with reference to the final protocol number and date. Details of the IRB/IEC's constitution, including names of its members and what function they perform on the committee (e.g., chairman, specialist, lay-member) should be documented by the Investigator.

During the study the Investigator should provide to the IRB/IEC all documents that are subject to review.
The Investigator will submit the protocol to the IRB/IEC and their written unconditional approval will be obtained before the start of the study.

The Investigator will provide all supportive literature (product data sheets) to the IRB/IEC for the protocol's review and approval. Verification of the IRB/IEC's unconditional approval of the protocol will be transmitted to the Investigator prior to the start of the study. This approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review.

The IRB/IEC must be informed by the Investigator of all subsequent protocol amendments and of unexpected SAEs occurring during the study that are likely to affect the safety of the Subjects or the conduct of the study. Approval for protocol amendments must be transmitted in writing by the Investigator.

The Investigator should provide the IRB/IEC with all relevant amendments or updates of the protocol and product information guidance. Also, the Investigator should provide written reports to the IRB/IEC annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the Subjects. A final report of study outcome, if required, should also be submitted by the Investigator to the IRB/IEC.

14.3 Informed Consent

The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, their legal representatives must be given ample opportunity to inquire about details of the study.

The Investigator or designee will explain the nature, purpose and risks of the study and provide the Subject with a copy of the study information sheet. The Subject will be given sufficient time to consider the study's implications before deciding whether to participate. Should the Investigators choose to produce their own information sheet, then the detail provided by the Sponsor information sheet should be regarded as the minimum written explanation required.

Consent forms must be in a language fully comprehensible to the prospective Subject. Informed consent will be documented by the use of an ICF approved by the IRB/IEC and signed by the Subject and the Investigator obtaining the consent. The ICF will also be annotated with the study Subject number.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the Subject's dated signature. The signature confirms the consent is based on information that has been understood. Each Subject's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities.

Should there be any amendments to the protocol that would directly affect the Subject's participation in the study, e.g., a change in any procedure, the ICF must be amended to incorporate this modification and the Subject must agree to sign this amended form indicating re-consent to participate in the study.

Subjects will be instructed that they are free to obtain further information from the Investigator at any time and that they are free to withdraw their consent/ assent and discontinue participation in the project at any time without prejudice.

The Subject will also be advised that access to medical records will be required and his/her general practitioner will be informed of the Subject's intention to participate in this study

14.4 Modification of Protocol

The Investigator should not implement any deviation from, or changes of, the protocol without documented approval/favourable opinion from the IRB/IEC of an amendment. The only exceptions are where necessary to eliminate an immediate hazard(s) to study Subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]). Non-substantial protocol amendments may or may not be

required to be submitted for approval/notification to the IRBs and regulatory agencies.

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted (according to national legislation):

- to the IRB for review and approval/favourable opinion,
- to the regulatory authority(ies).

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the Investigator. The Investigator will submit protocol amendments, as necessary, to the appropriate IRB/IEC.

All protocol amendments must be clearly documented using standard procedures and must be signed and dated by the Investigator.

15.0 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study, but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC, but will not result in protocol amendments.

15.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain Subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the Subject (or the Subject's legal guardian), except as necessary for monitoring and auditing by the FDA or the IRB/IEC.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

15.2 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and 21 CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original Investigator-signed Investigator agreement page of the protocol
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the Subject or legal guardian

15.3 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of Subjects begins.

15.4 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

15.5 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of AEs and SAEs according to the time line and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

15.6 Investigator's Final Report

Upon completion of the study, the Investigator should provide the IRB/IEC with a summary of the study's outcome and the regulatory authority(ies) with any reports required.

16.0 DATA HANDLING AND RECORD KEEPING

16.1 Completion of Case Report Forms

The Investigator will be provided with detailed CRF completion guidelines that will identify the required data points to be collected, how to document them, and when the data should be documented.

It is the responsibility of the Investigator to maintain adequate and accurate CRFs to record (according to the CRF completion guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All CRFs should be fully completed to ensure accurate data interpretation.

16.2 Archiving

According to ICH-GCP, the documents which should be archived are 'essential documents' which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.

Source documentation must also be archived. This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or CRFs and research related records held in support departments. All hard copies of source documents must be retained. If electronic records of documents exist these must be backed up and retained with the hard copies.

17.0 FINANCING AND INSURANCE

The costs necessary to perform the study will be the responsibility of the Investigator and Sponsor

18.0 PUBLICATION POLICY

Study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Investigator will be responsible for these activities and will determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues.

19.0 REFERENCES

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APPENDICES

APPENDIX 1: STUDY SCHEDULE OF EVENTS

Schedule of Events:

Evaluations	Screening/ Baseline	Day 28 (+/-14 days)	Week 12 (+/- 14 days)	Week 24 (+/- 14 days)	Week 36 (+/- 14 days)	Week 48/EOS/Early Termination (+/- 14 days)
Inclusion/exclusion criteria	X					
Demography[a]	X					
HIV viral load	X	X	X	X	X	X
CD4 count	X (within 3 months)					X
Height, Weight, BMI[b]	X	X	X	X	X	X
Physical examination, including other signs and symptoms	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X
Hematology (CBC with differential)	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X
Blood sampling for PK[d]		X				
Adverse events[e]	X	X	X	X	X	X
Pittsburgh Sleep Quality Index	X					X
WPAI Questionnaire	X					X
Drug Treatment Switch	X					

[a] Demographic information consists of age, gender, race, year of HIV diagnosis and ethnicity

[b] Subject's height must be recorded at Screening; weight should be recorded at every examination and body mass index (BMI) calculated.

[c] Vital signs include pulse, systolic and diastolic blood pressure, respiratory rate, and body temperature.

[d]Plasma samples for PK assessments will be collected before dosing at -0.5 hr (time 0) and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours afterdosing on day 28 (+/- 14 days) in the PK cohort. Subjects may be asked to return for an unscheduled visit to test/retest PK samples if the initial data is found to be invalid

[e] Adverse events will be assessed beginning at enrolment (date of signed informed consent) and up to last dose of study drug. Treatment-emergent AEs will be assessed during the dosing period.

APPENDIX 2: INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR STUDY ACKNOWLEDGEMENT / PROTOCOL SIGNATURE PAGE

Investigator's Statement:

I have read and understand the foregoing clinical study protocol entitled, "An open label study evaluating the safety and efficacy of switching from rilpivirine/emtricitabine/tenofovir alafenamide in combination with dolutegravir, to bictegravir/emtricitabine/tenofovir alafenamide in combination with doravirine, in male HIV+ subjects ≥ 45 years with multi-drug resistant virus and virologic suppression (documented with at least one viral load result ≤ 50 copies per mL) during the last 6 months on current therapy. **Protocol No.: BETD-001.**

I understand and recognize its confidentiality and agree to conduct this study as described in the protocol, in compliance with Good Clinical Practices (GCP), designated standard operating procedures, all applicable regulations of the country in which the study is being conducted, and within the principles of the current version of the Declaration of Helsinki.

Investigator's Name (please print)	Investigator's Title
Date (dd-mm-yyyy)	Investigator's Signature

APPENDIX 3: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The United States of America (USA) Common Terminology Criteria for Adverse Events, version 5.0 can be found online at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX 4: DATA SHEET FOR BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (BIKTARVY®)

https://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf

APPENDIX 5: DATA SHEET FOR DORAVIRINE (PIFELTRO ®)

https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_pi.pdf

APPENDIX 6: PITTSBURGH SLEEP QUALITY INDEX

https://www.opapc.com/uploads/documents/PSQI.pdf

APPENDIX 7: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE

http://oml.eular.org/sysModules/obxOML/docs/id_98/WPAI-GH_English_US_V2.pdf