Chelsea and Westminster Hospital
NHS Foundation Trust

CLINICAL TRIAL PROTOCOL

Pharmacokinetics of plasma doravirine once daily over 72 hours following drug intake cessation in healthy volunteers

Protocol Number:	**CRF001**
Version and Date:	Version 1.6 dated 06 June 2019
EudraCT:	2019-000978-33
IRAS number:	261913
Principal Chief Investigator:	Dr Marta Boffito St. Stephen's Centre Chelsea and Westminster Hospital 369 Fulham Road, London SW10 9NH
Sponsor:	Chelsea and Westminster Hospital NHS Foundation Trust 369 Fulham Road London SW10 9NH

Protocol Approval: _____ _____

Dr Marta Boffito Date

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

Synopsis

Study title	Pharmacokinetics of plasma doravirine once daily over 72 hours following drug intake cessation in healthy volunteers.
Phase of study	Phase I
Protocol Number	CRF001
EudraCT	2019-000978-33
Name of active ingredients	Doravirine
Name of Investigational Product	Pifeltro®
Objectives	The objectives of this study are: **Primary** -To assess the pharmacokinetics of plasma doravirine once daily over 72 hours following drug intake cessation at steady-state in healthy volunteers **Secondary** -To investigate the safety and tolerability of doravirine -To investigate the association between genetic polymorphisms in drug disposition genes and drug exposure **Exploratory** -To investigate the impact of doravirine intake on platelet function and markers of platelet and endothelial cell activation -To investigate of the metabolic changes associated with short term doravirine intake in healthy volunteers
Study design	10 days (excluding screening and follow up), open label, pharmacokinetic study
Indication	Not applicable
Methodology	Measurements of steady state plasma pharmacokinetic profile and pharmacokinetic forgiveness of doravirine
Planned sample size	Up to 24 healthy volunteers may be enrolled at baseline in order to achieve 14 completing the study
Summary of eligibility criteria	Healthy participants as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical

	laboratory evaluations will be eligible to participate in the study. Women of childbearing potential must not be nursing or pregnant. Women of childbearing potential must have a negative pregnancy test at screening
Number of study centres	One
Duration of treatment	10 days (excluding screening and follow up visits)
Dose and route of administration	All participants will be administered Pifeltro® 100 mg once daily for 7 days
Criteria for evaluation	Pharmacokinetic parameters of doravirine will be evaluated on blood drawn on day 7 (at 0 (pre-dose), 2, 4, 8, 12 hours post last dose), and on days 8 to 10 at 24, 30, 36, 48, 54, 60, and 72 hours post last dose Safety and tolerability of the study medication will also be assessed by questions, physical examination and laboratory parameters. These will be performed at regular intervals during the drug study
Primary endpoint	Steady state plasma concentrations of doravirine after drug intake cessation up to 72 hours post-dose
Secondary end points	Safety and tolerability of the studied drug Relationship between genetic polymorphisms and exposure to the studied drugs
Exploratory end points	Effect of short term doravirine intake upon platelet function and markers Investigation of the metabolic changes associated with short term doravirine intake in healthy volunteers.

General Study Information

Name of sponsor:	Chelsea and Westminster Hospital NHS Foundation Trust 369 Fulham Road LondonSW10 9NH
Chief investigator:	Dr Marta Boffito Chelsea and Westminster Hospital 369 Fulham Road, London SW10 9NH Phone 0208 846 6507
Laboratory facilities: Biochemistry & Haematology	 Imperial College NHS Foundation Trust Pathology Laboratory Chelsea and Westminster Hospital 369 Fulham Road London SW10 9NH
Virology & Hepatitis	Imperial College NHS Foundation Trust Dept. of Infection & Immunity 9th Floor Laboratory Block Charing Cross Hospital Fulham Palace Road London W6 8RF
Pharmacokinetics and metabolomics	Jefferies Research Trust Laboratories Wright-Fleming Institute Imperial College London Dept. of Medicine, St Mary's Campus Norfolk Place London W2 1PG
Pharmacogenetics	Pharmacology Research Laboratories University of Liverpool Block H – First floor 70 Pembroke Place Liverpool L69 3GF
Platelet/endothelium	Dr Mike Emerson National Heart and Lung Institute

	Sir Alexander Fleming Building South Kensington Campus Imperial College London Exhibition Road London SW7 2AZ
Processing and Shipping PK & PG samples:	HIV/GUM Laboratory St Stephen's Centre Chelsea and Westminster Hospital 369 Fulham Road London SW10 9NH
Medical expertise:	Dr Marta Boffito St Stephens Centre Chelsea and Westminster Hospital 369 Fulham Road London SW10 9NH Phone 0208 846 6507
Data management and Statistics:	Research and Development Office Chelsea and Westminster Hospital NHS Foundation Trust Unit G2, Harbour Yard Chelsea Harbour London SW10 0XD
Monitor:	Research and Development Office Chelsea and Westminster Hospital NHS Foundation Trust Unit G2, Harbour Yard Chelsea Harbour London SW10 0XD Phone 020 3315 6825 Email research.development@chelwest.nhs.uk

List of abbreviations and definitions of terms

ACTG	AIDS Clinical Trial Group
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AUC	Area Under the concentration-time Curve
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body Mass Index
C_{max}	Maximum concentration
CM	Concomitant Medication
CRF	Case Report Form
C_{trough}	Trough concentration
CYP450	Cytochrome P450
DAIDS	Division of AIDS
ECG	Electrocardiogram
FBC	Full blood count
GCP	Good Clinical Practice
GP	General Practitioner
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICH-GCP	International conference of harmonization good clinical practice
IMP	Investigational Medicinal Product
LFT	Liver function test
MHRA	Medicines and Healthcare products Regulatory Agency
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OD	Once daily
PG	Pharmacogenetic
PI	Protease inhibitors
PK	Pharmacokinetic
PLWH	People living with HIV
SAE	Serious Adverse Event
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOPS	The over-volunteering prevention scheme
$T_{1/2}$	Half-life
UK	United Kingdom
U&E	Urea and Electrolytes
WOCBP	Women of Child Bearing Potential

Contents

Background

1.1 Introduction

The administration of combination antiretroviral therapy (cART) to HIV-infected patients has been associated with a dramatic reduction in AIDS-related morbidity and mortality [1-3].

The key to successful HIV drug treatment is adhering to the prescribed combination every day [2]. The approval of single tablet combinations (STRs) provides HIV care providers with a “one tablet once a day” therapy, making adherence much easier for patients.

However, in HIV therapy, successful adherence also means attention to intervals between doses or dietary restrictions. Ideally, to guarantee long-term virological response, HIV-infected patients should take their cART every day at the same time. However, cART is for life and doses can be forgotten or delayed.

1.2 Background and study rationale

A drug’s persistence in plasma or in cells depends on its half-life. Long half-life antiretroviral agents may allow for missed or delayed doses, if concentrations are maintained at therapeutic levels until the next dose is taken. However, data on drug persistence are limited and whether drug doses can be omitted and dosing delayed is unknown [1].

Knowledge of the length of time the drugs last would increase the confidence of doctors in this combination [1]. Therefore a study investigating the pharmacokinetic “forgiveness” of the new non nucleoside reverse transcriptase inhibitor doravirine would provide information on how to advise HIV infected patients on delayed and missed doses. Doravirine has been recently approved to treat HIV infection and it is available as a single agent (Pifeltro®) and as a fixed dose combination with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) (Delstrigo) [2]. The tail pharmacokinetics of tenofovir and lamivudine has been extensively characterised.

Therefore in this study we will investigate the persistence of doravirine only, thus minimising the exposure of participants to medicinal agents.

Rationale for pharmacogenetic analysis

Pharmacogenetics holds promise in HIV treatment because of the complexity and potential toxicity of multi antiretroviral drug therapies that are prescribed for long periods. Thus far, few candidate genes have been examined for a limited number of allelic variants, but a number of confirmed associations have already emerged.

From a public health perspective, as antiretroviral medications become increasingly available to racially and ethnically diverse populations worldwide, understanding the genetic structures of each population may allow us to anticipate the impact of adverse responses, even in groups that were not represented in drug registration trials.

The existing literature on pharmacogenetic determinants of antiretroviral drug exposure, drug toxicity, as well as genetic markers associated with the rate of disease progression underline the recent advances which occurred in the past few years. However, it is expected that larger-scale comprehensive genome approaches will profoundly change the landscape of knowledge in the future. Additional studies are needed to assess the implications for long-term responses to antiretroviral agents.

For this reason we plan to collect a single blood sample from each participant in our intensive pharmacokinetic studies, such as this one, in order to be able to investigate the association between genetic polymorphisms in drug disposition genes (such as those encoding for cytochrome P450 isoenzymes or transmembrane transporters) and drug exposure. A candidate gene approach will be utilised to examine loci of interest. This procedure will provide potentially important information on genetic influences on plasma drug concentrations and give insight into how to improve the management of HIV-infected patients by individualising therapy. These studies will not be powered for genetic associations but will enable us to build a data base of genotype-phenotype. Prospective genetic studies would need to be planned based on these preliminary data.

Rationale for exploratory endpoints:

Platelet and endothelial function

Cardiovascular risks, specifically platelet-driven events such as myocardial infarction, are more prevalent in people living with HIV. The causes of increased risk are unclear but a number of studies have shown risk to be associated with antiretroviral therapy. There is also evidence that some drug regimens impact the cardiovascular system to a greater extent than others. Understanding the cardiovascular risk profile of antiretrovirals delivers information on their tolerability that could ultimately reduce multi-morbidity in PLWH. The current study provides an opportunity to investigate acute changes in platelet and endothelial cell function that occur during doravirine administration. We shall isolate platelets and plasma from blood and conduct light transmission aggregometry assays as well as flow cytometric assays to measure markers of platelet and endothelial activation. These studies are intended to be preliminary and are intended to generate data to justify subsequent studies in older PLWH and patients with cardiovascular conditions in order to better understand the impact of doravirine-containing therapies relative to alternative antiretroviral regimens in relevant, at-risk populations.

Metabolomics

Metabolomics can be used to profile the maximum number of metabolites found within an organism tissue, cell or biofluids, enabling detailed mapping of perturbed pathways involved in ART drug response. This approach has the potential to unravel on- and off-target effects of ART and further our understanding of mechanisms of action, metabolism and toxicities. With new safer antiretrovirals becoming available, it is important to understand what the drug effect could be on certain metabolic pathways, especially in view of people living with HIV ageing and needing access to such safer drugs. We therefore aim to carry out liquid chromatography mass spectrometry (LC-MS) based metabolomics analysis on plasma and urine samples from the healthy volunteers enrolled in the study before drug intake and when the drug has reached steady-state to investigate the metabolic changes associated with short term doravirine intake. The twelve plasma samples obtained primarily for PK samples may also be used for these analyses.

These studies will not be powered for drug/metabolomics changes associations but will enable us to build a data base on drug/metabolomics changes. Prospective studies would need to be planned based on these preliminary data.

2 Trial Objectives

2.1 Primary

- To assess the pharmacokinetics of plasma doravirine once daily over 72 hours following drug intake cessation at steady-state in healthy volunteers.

2.2 Secondary

- To investigate the safety and tolerability of doravirine.
- To investigate the association between genetic polymorphisms in drug disposition genes and drug exposure.

2.3 Exploratory

- To investigate the impact of doravirine intake on platelet function and markers of platelet and endothelial cell activation.
- To investigate of the metabolic changes associated with short term doravirine intake in healthy volunteers.

3 Trial Design

3.1 Endpoints

Primary endpoint

- Steady state plasma concentrations of doravirine after drug intake cessation up to 72 hours post-dose.

Secondary endpoints

- Safety and tolerability of the studied drug.
- Relationship between genetic polymorphisms and exposure to the studied drugs.

Exploratory endpoints

- Impact of doravirine intake on platelet function and markers of platelet and endothelial cell activation.
- Investigation of the metabolic changes associated with short term doravirine intake in healthy volunteers.

3.2 Study design

This study is a 10 day (excluding screening and follow up), open label, pharmacokinetic study.

Table 1: Study design

Study Visit	Day	Study procedures
Screening	Day -28 to 0	Written informed consent, demographics, medical history and co-medications (CMs) review. Physical examination, height, weight, vital signs (including temperature, blood pressure, heart rate and respiratory rate), ECG, urinalysis (macro-

		analysis, drug screen and pregnancy test for WOCBP), HIV/HBV/HCV testing, safety bloods (see appendix 1) and registration of TOPS database. Fulfil all inclusion criteria.
Baseline **<u>Start doravirine 100 mg</u>**	Day 1 (morning)	Vital signs, safety bloods, urinalysis (macro-analysis, drug screen and pregnancy test for WOCBP) First drug dose in a fasted state (one tablet once daily), witnessed drug intake, concomitant medication check and adverse events (AE review). PG blood sample collection (can be collected any visit after Day 1) Platelet and metabolomics (plasma, urine and faeces) pre-dose sampling
Day 2-6 Drug self-administration	Day 2-6	All participants will be instructed to take their doravirine dose at home in the morning (fasting)
Day 7-10 PK Phase	Day 7 Day 8 Day 9 Day 10	All participants will be dosed in the unit fasting, witnessed drug intake, vital signs, safety bloods, urinalysis (macro-analysis, drug screen and pregnancy test for WOCBP), review of CM and AE. Cannulas will be placed when possible/preferred. Platelet and metabolomics (plasma, urine and faeces) post-dose sampling. Blood for PK assessment will be drawn pre-dose and 2,4,8,12 hrs post dose AND 24, 30, 36 hours post dose 48, 54, 60 hours post dose 72 hours post dose These PK samples may also be used for metabolomics analyses.
Follow up visit **(10-13 days after last PK blood sample)**	Day 20 to 23	Safety bloods, vital signs, review of CM and AEs Platelet and metabolomics (plasma, urine and faeces) post-dose sampling

3.3 Randomisation and blinding

Not applicable.

4 Participant population

4.1 Number of participants and participant selection

Healthy male and female volunteers as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations will be eligible to participate in the study. Women of childbearing potential must not be nursing or pregnant.

No formal size calculation was performed. Fourteen (14) participants completed are considered sufficient to allow for relevant conclusions to be drawn, given experience from similar studies conducted previously. Up to 24 participants will be enrolled to achieve this.

4.2 Inclusion criteria

Participants must meet all of the following inclusion criteria within 28 days prior to the baseline visit:

1. The ability to understand and sign a written informed consent form, prior to participation in any screening procedures and must be willing to comply with all study requirements

2. Male or non-pregnant, non-lactating females.

3. Between 18 to 65 years, inclusive

4. Body Mass Index (BMI) of 18 to 35 kg/m^2, inclusive

5. ALT, alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). A single repeat is allowed for eligibility determination.

6. Women of childbearing potential (WOCBP – definition in Appendix 4) must be using an adequate method of contraception to avoid pregnancy throughout the study and for a period of at least 4 weeks after the study.

   A female may be eligible to enter and participate in the study if she:

   a. is of non-child-bearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or,
   b. is of child-bearing potential with a negative pregnancy test at both Screening and day 1 and agrees to use one of the following methods of contraception to avoid pregnancy:
      i. Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of IP, throughout the study, and for at least 4 weeks after discontinuation of all study medications. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the patient;
      ii. Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide);
      iii. Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion, see protocol appendix 4 for an example listing of approved IUDs);

iv. Male partner sterilisation confirmed prior to the female subject's entry into the study, and this male is the sole partner for that subject;

v. Approved hormonal contraception (see protocol appendix 4 for a listing of examples of approved hormonal contraception) plus male condom;

vi. Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 4 weeks after discontinuation of IP.

7. Men who have partners who are women of childbearing potential (WOCBP – definition in Appendix 4) must be using an adequate method of contraception to avoid pregnancy in their partner throughout the study and for a period of at least 4 weeks after the study (see inclusion criteria 6);

a. Complete abstinence from penile-vaginal intercourse. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the patient;

b. Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide);

c. 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 4 for an example listing of approved IUDs);

d. Sterilisation confirmed prior to the subject's entry into the study

e. Approved hormonal contraception used by female partner (see protocol appendix 4 for a listing of examples of approved hormonal contraception) plus male condom;

f. Any other method with published data showing that the expected failure rate is <1% per year and not containing hormones.

Any contraception method must be used consistently, in accordance with the approved product label and for at least four weeks after discontinuation of IMP.

8. Willing to consent to their personal details being entered onto the TOPS database

9. Willing to provide proof of identity by photographic ID at screen and any subsequent visit

10. Registered with a GP in the UK

4.3 Exclusion criteria

Participants who meet any of the following exclusion criteria are <u>not</u> to be enrolled in this study;

1. Any clinically significant acute or chronic medical illness

2. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations

3. Positive blood screen for hepatitis B surface antigen or C antibody

4. Positive blood screen for HIV-1 or 2 by antibody/antigen assay

5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

6. History or presence of allergy to the study drugs and their components

7. Current or recent (within three months) gastrointestinal disease

8. Known intolerance of lactose monohydrate, sunset yellow aluminium lake (E110), and patients with galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

9. Clinically relevant alcohol or drug use (positive urine drug screen) or history of alcohol or drug use considered by the Investigator to be sufficient to hinder compliance with treatment, follow-up procedures or evaluation of adverse events. Smoking is permitted, but tobacco intake should remain consistent throughout the study

10. Exposure to any investigational drug (or placebo) or participation in a clinical study involving the donation of blood samples within three months of first dose of study drug

11. Use of any other drugs (unless approved by the Investigator), including over-the-counter medications and herbal preparations, within two weeks prior to first dose of study drug, unless approved/prescribed by the Principal Investigator as known not to interact with study drugs.

12. Females of childbearing potential without the use of effective non-hormonal birth control methods, or not willing to continue practising these birth control methods for at least four weeks after the end of the treatment period

4.4 Duration of involvement

Total duration of involvement in the study is 10 days plus a screening visit within 28 days prior to commencement at day 1 and follow-up visit between study days 20 and 23 (approximately 14 days after the last blood test).

During this time participants will be instructed in the information leaflet to refrain from certain activities, which can potentially affect the rate of drug metabolism:

- Strenuous exercise, contact sports and sunbathing
- Drinking alcohol-containing beverages for two days prior to Days 7 and during Days 7-10. Alcohol is prohibited whilst a participant is in the unit
- Drinking or eating any grapefruit, Seville oranges or grapefruit and Seville orange containing products for two days prior to Day 7 and during Days 7-10.
- Drinking caffeine-containing beverages for two days prior to Day 7 and during Days 7-10.

Smoking whilst residing at the clinical facility is not allowed.

4.5 Withdrawal of patients and discontinuation criteria

Participants may be asked whether they are interested in taking part into the study while all study participants have already been identified. This would make the participant a reserve and they will be contacted to take part into the whole study only if a study participant withdraws from the study and the number of subjects completing the study is considered insufficient. This means that they may only attend the screening visit and be remunerated only for their limited attendance. Details on this will be further explained to the participant by study staff in these circumstances.

4.5.1 Criteria for premature withdrawal

Participants have the right to withdraw from the study at any time for any reason. The investigator may also withdraw participants from the study or decide to discontinue medication dosing in the event of inter-current illness, AEs, protocol violations, administrative reasons or other reasons. An excessive rate of withdrawals can render the study impossible to interpret; therefore unnecessary withdrawal of participants should be avoided.

In all cases, the date and reasons for withdrawal or discontinuation of medication will be clearly stated on the participant's CRF. If the reason for removal of a participant from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF. Withdrawn participants may be replaced at the discretion of the Investigator.

4.6 Follow-up of abnormal laboratory test values

In the event of unexplained abnormal laboratory test values, the tests should be repeated and followed up as per medical need, until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

5 Definition of end of trial

The end of the trial is defined as the date of the last visit of the last participant undergoing the trial.

6 Treatment of participants

6.1 Study treatment regimen

Participants will be administered:

Pifeltro® (doravirine 100 mg) once daily for 7 days

All IMPs will be labelled for clinical trial use using MHRA approved annex 13 compliant labels.

7 Study IMP

Refer to current version of Pifeltro® summary of product characteristics for full IMP information and administration instructions.

8 Pharmacokinetics and pharmacodynamics

8.1 Pharmacokinetics

Absorption

The pharmacokinetics of doravirine was studied in healthy subjects and HIV-1-infected subjects. Doravirine pharmacokinetics is similar in healthy subjects and HIV-1-infected subjects. Steady state was generally achieved by Day 2 of once-daily dosing, with accumulation ratios of 1.2 to 1.4 for AUC_{0-24}, C_{max}, and C_{24}. Doravirine steady state pharmacokinetics following administration of 100 mg once daily to HIV-1 infected subjects, based on a population pharmacokinetics analysis, are provided below.

Parameter GM (%CV)	AUC_{0-24} µM hr	C_{max} µM	C_{24} nM
Doravirine 100 mg once daily	37.8 (29)	2.26 (19)	930 (63)
GM: geometric mean, % CV: Geometric coefficient of variation			

Following oral dosing, peak plasma concentrations are achieved 2 hours after dosing. Doravirine has an estimated absolute bioavailability of approximately 64% for the 100 mg tablet.

Effect of food on oral absorption

The administration of a single doravirine tablet with a high-fat meal to healthy subjects resulted in a 16% and 36% increase in doravirine AUC and C_{24}, respectively, while C_{max} was not significantly affected.

Distribution

Based on administration of an IV microdose, the volume of distribution of doravirine is 60.5 L. Doravirine is approximately 76% bound to plasma proteins.

Biotransformation

Based on in vitro data, doravirine is primarily metabolized by CYP3A.

Elimination

Doravirine has a terminal half-life ($t_{1/2}$) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism mediated by CYP3A4. Biliary excretion of unchanged medicinal product may contribute to the elimination of doravirine, but this elimination route is not expected to be significant. Excretion of unchanged medicinal product via urinary excretion is minor.

Renal impairment

Renal excretion of doravirine is minor. In a study comparing 8 subjects with severe renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 31% higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, which included subjects with CrCl between 17 and 317 mL/min, renal function did not have a clinically relevant effect on doravirine pharmacokinetics. No dose adjustment is required in patients with mild, moderate or

severe renal impairment. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis (see section 4.2).

Hepatic impairment

Doravirine is primarily metabolized and eliminated by the liver. There was no clinically relevant difference in the pharmacokinetics of doravirine in a study comparing 8 subjects with moderate hepatic impairment (classified as Child-Pugh score B primarily due to increased encephalopathy and ascites scores) to 8 subjects without hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) (see section 4.2).

Elderly

Although a limited number of subjects aged 65 years and over has been included (n=36), no clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis. No dose adjustment is required.

Gender

No clinically relevant pharmacokinetic differences have been identified between men and women for doravirine.

Race

No clinically relevant racial differences in the pharmacokinetics of doravirine have been identified based on a population pharmacokinetic analysis of doravirine in healthy and HIV-1-infected subjects.

8.2 Undesirable effects

Summary of the safety profile: The most frequently reported adverse reactions considered possibly or probably related to doravirine were nausea (4%) and headache (3%).

Tabulated summary of adverse reactions: The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Tabulated summary of adverse reactions associated with doravirine used in combination with other antiretrovirals:

Frequency	**Adverse reactions**
Infections and infestations	
Rare	rash pustular
Metabolism and nutrition disorders	
Uncommon	hypophosphataemia,
Rare	hypomagnesaemia
Psychiatric disorders	
Common	abnormal dreams, insomnia[1]
Uncommon	nightmare, depression[2], anxiety[3], irritability, confusional state, suicidal ideation

Rare	aggression, hallucination, adjustment disorder, mood altered, somnambulism
Nervous system disorders	
Common	headache, dizziness, somnolence
Uncommon	disturbance in attention, memory impairment, paraesthesia, hypertonia, poor quality sleep
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Rare	dyspnoea, tonsillar hypertrophy
Gastrointestinal disorders	
Common	nausea, diarrhoea, flatulence, abdominal pain[4], vomiting
Uncommon	constipation, abdominal discomfort[5], abdominal distension, dyspepsia, faeces soft[6], gastrointestinal motility disorder[7]
Rare	rectal tenesmus
Skin and subcutaneous tissue disorders	
Common	rash[8]
Uncommon	pruritus
Rare	dermatitis allergic, rosacea
Musculoskeletal and connective tissue disorders	
Uncommon	myalgia, arthralgia
Rare	musculoskeletal pain
Renal and urinary disorders	
Rare	acute kidney injury, renal disorder, calculus urinary, nephrolithiasis
General disorders and administration site conditions	
Common	fatigue
Uncommon	asthenia, malaise
Rare	chest pain, chills, pain, thirst
Investigations	
Common	alanine aminotransferase increased[9]
Uncommon	lipase increased, aspartate aminotransferase increased, amylase increased, haemoglobin decreased
Rare	blood creatine phosphokinase increased

[1]insomnia includes: insomnia, initial insomnia and sleep disorder
[2]depression includes: depression, depressed mood, major depression, and persistent depressive disorder
[3]anxiety includes: anxiety and generalized anxiety disorder
[4]abdominal pain includes: abdominal pain, and abdominal pain upper
[5]abdominal discomfort includes: abdominal discomfort, and epigastric discomfort
[6]faeces soft includes: faeces soft and abnormal faeces
[7]gastrointestinal motility disorder includes: gastrointestinal motility disorder, and frequent bowel movements
[8]rash includes: rash, rash macular, rash erythematous, rash generalized, rash maculo-papular, rash papular, and urticarial
[9] alanine aminotransferase increased includes: alanine aminotransferase increased and hepatocellular injury

For full specifications on Pifeltro® please refer to the updated SmPCs [3].

Prior and Concomitant Therapy

All illegal drugs are forbidden

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during the study unless they are approved / prescribed by the Investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

8.3 Treatment compliance

Participants will be requested to return to site any unused Pifeltro® tablets on day 7. Site staff will count the IMP and this will be recorded in the source.

Furthermore, adherence to study drugs will be evaluated on Day 7 and ETV (if required), by study staff – by direct questioning of dosing schedules, missed and late doses. This will be documented in the participant's source document and CRF.

8.4 Provision of treatment after the end of the trial

All study participants are healthy volunteers, and no medication will be provided after the final dose of study drugs. Post study follow up will occur between days 20 and 23 for monitoring of vital signs, haematology with a differential and clotting screen, chemistry panel, concomitant medications, and an adverse event check.

9 Visit schedule and procedures

9.1 Assessments at each visit

The schedule of assessments is summarised in the study flow chart in Appendix 1. Visits may take place up to 48 hours from that specified at the discretion of the investigator.

Screening

Each participant must sign an Informed Consent Form prior to the conduct of any screening procedures. They will sign three informed consent forms and keep one. As part of the consent procedure participants will also be asked to consent to their personal details being entered onto TOPS. Participants will be given the opportunity to ask any questions regarding the trial at this stage.

Screening evaluations will be used to determine the eligibility of each candidate for study enrolment.

The screening visit will evaluate:

- Demographic details, including age, gender and ethnic background.
- Full medical, drug and social history
- Physical examination including weight, height, and vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- ECG

- Chemistry panel (see Appendix 1)
- Haematology with a differential and clotting screen (Appendix 1)
- HIV antibody testing
- Hepatitis B and C screening
- Urinalysis (including macro analysis)
- Drug screen (urine)
- Pregnancy test for WOCBP (urine)
- Registration of TOPS database
- Concomitant medications

GP verification of medical history

A medical history questionnaire should be sent to all participants' GPs for verification of medical history. This information is reviewed by the Investigator as part of the medical history evaluation. If the completed questionnaire is not received from the GP, then the available information regarding the participant should be reviewed by the Principal Investigator. The Principal Investigator will assess this information and decide whether they are sufficiently confident that the inclusion and exclusion criteria are met and whether the participant may be enrolled into the research trial. This decision must be documented in writing BEFORE the participant is dosed. Copies of sent GP letters and returned confirmation of medical history must be filed in each participant's source documentation.

Randomisation

Not applicable

Baseline visit, Day 1

Participants will attend the unit in the morning. They will be asked to fast for 8 hours overnight prior to attending.

The following evaluations will be performed in the morning of Day 1, before study medication dosing:

- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Haematology with a differential and clotting screen (Appendix 1)
- Chemistry panel (Appendix 1)
- Urinalysis (including macro analysis)
- Pregnancy test for WOCBP (urine)
- Drug screen (urine)
- Concomitant medications
- Review of AEs
- Witnessed dosing

Blood collection (one 4mL EDTA bottle) for the pharmacogenetic analysis will occur on Day 1 (or on any subsequent study day) only for enrolled participants who signed the pharmacogenetic analysis informed consent.

Pre-dose: Platelet/endothelium sample: see Appendix 3 for details

Pre-dose: Metabolomics: plasma, urine and faeces: see Appendix 3 for details

A Pifeltro® tablet will be administered in a fasting state (no food for at least 2 hours before dosing, only water is allowed), along with 240 mL of water. This will set the nominal time of dosing. Subjects will be instructed to administer Pifeltro® at home in the morning on all other days (5 days in total) in the same way.

Day 7

Participants will attend the Unit in the morning. They will be asked to fast for 8 hours overnight prior to attending.

The following evaluations will also be performed in the morning of Day 7, before study medication dosing:

- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Haematology with a differential and clotting screen (Appendix 1)
- Chemistry panel (Appendix 1)
- Urinalysis (including macro analysis)
- Pregnancy test for WOCBP (urine)
- Drug screen (urine)
- Concomitant medications
- Review of AEs
- Witnessed dosing

A Pifeltro® tablet will be administered in a fasting state, along with 240 ml of water. This will set the nominal time of dosing.

Intensive Pharmacokinetic Visits (Days 7 to 10)

Participants will be admitted to the unit in the morning on days 7, 8, 9 and 10.

On day 7, they will remain in the unit for approximately 14 hours and they will be asked to fast for 8 hours overnight prior to attending on day 7.

Serial blood specimens will be obtained from each subject for determining plasma drug concentrations at the following time points: pre-dose and 2, 4, 8, 12 hours post dose. All plus/minus 10 minutes.

From two hours after administration of study drug, subjects may resume water intake. A standardised lunch will be served at least four hours after dosing. After lunch, subjects may resume their usual diet. The start time of lunch served will be recorded on the CRF.

The exact time of intake of study medication will be recorded on the CRF. Subjects should remain in a semi-recumbent position until four hours post dose.

Post-dose: Platelet/endothelium sample: see Appendix 3 for details

Post-dose: Metabolomics: plasma, urine and faeces: see Appendix 3 for details

Patients will be able to leave the unit after the 12-hour sample to return the following morning.

On days 8, 9, and 10 they will undergo blood sampling at the following time-points:

24, 30, 36, 48, 54, 60, 72 hours post dose. All plus/minus 10 minutes.

And the following will take place:

- Review of AEs
- Concomitant medication check

Follow up visit (day 20 to 23)

Participants will return to the unit on one occasion between days 20 to 23 inclusive, they will be asked to fast for 8 hours overnight prior to attending and the following evaluations will be performed:

- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Haematology with a differential and clotting screen (Appendix 1)
- Chemistry panel (Appendix 1).
- Concomitant medications
- Review of AEs

Follow-up: Platelet/endothelium sample: see Appendix 3 for details

Follow-up: Metabolomics: plasma, urine and faeces: see Appendix 3 for details

Early termination visit

In case of early termination, participants should attend the unit for an early termination visit within one week (or otherwise as the investigator believes appropriate). Participants will be asked to fast for 8 hours overnight prior to attending, when possible.

During these visits the following evaluations will be performed:

- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Haematology with a differential and clotting screen (Appendix 1)
- Chemistry panel (Appendix 1).
- Concomitant medications
- Review of AEs and adverse event check
- Pregnancy test
- ECG
- Adherence questioning (if required)

The reason for the early termination of the participant should be clearly documented on the participant's CRF. The participant will not then be required to attend for a follow up visit unless deemed necessary in the opinion of the investigator (e.g. due to adverse event follow up).

10 Statistical analysis

10.1 Participant numbers

10.1.1 Sample size

This is an exploratory study and, as such, no formal sample size calculation was performed. Fourteen (14) participants completing the study will allow for relevant conclusions.

10.1.2 Criteria for evaluation

All eligible participants who complete the pharmacokinetic assessment will be included in the final data analysis and all baselined participants will be included in the safety analysis.

10.2 Statistical methods

Statistical analysis will be descriptive.

10.2.1 Safety parameters

All patients, whether withdrawn prematurely or not, will be included in the safety analysis.

All safety data and adverse events will be summarised.

10.2.2 Pharmacokinetic parameters

Summary statistics will be provided for all pharmacokinetic parameters calculated.

The pharmacokinetic parameters calculated for doravirine will be trough concentration (C_{trough}), defined as the concentration at 24 hours after the observed drug dose, the maximum observed plasma concentration (C_{max}), elimination half-life ($t_{1/2}$ – to last measurable time-point), time point at C_{max} (T_{max}), and total drug exposure, expressed as the area under the plasma concentration–time curve from 0–24 hours after dosing ($AUC_{0–24h}$) and 0-72 hours (AUC_{0-72h}).

Coefficient of variation (CV=mean/SD*100) will be calculated at all time-points and for the measured parameters.

All pharmacokinetic parameters will be calculated using non-compartmental modelling techniques (WinNonlin®). All statistical calculations will be performed an analysed using SAS (version 9.1).

10.3 Criteria for termination of the trial

The sponsor or investigator may terminate either part of, or the entire study for safety or administrative reasons. A written statement fully documenting the reasons for such a termination will be provided to the Ethics Committee and the Regulatory Authority as appropriate.

11 Adverse Events

11.1 Definitions

An adverse event is any untoward medical occurrence (any new untoward medical occurrence or worsening of a pre-existing medical condition) in a clinical investigation subject administered a study drug 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 temporarily 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 participant, and any remedial action taken, will be recorded in the participant's CRF and should be verifiable in the participant'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 treatment (unrelated, unlikely, possible, probable, and definite).

All participants 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 (planned prior to the participant's enrolment into the study) need not 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.

11.2 Assessment of intensity

Severity should be recorded and graded according to the DAIDS Clinical Trial Group (ACTG) Grading Scale (Appendix 2).

Note: There is a distinction between the gravity 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 met one of the criteria for serious events.

11.3 Assessment of causality

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following (Related means there is a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship):

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

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

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by participant'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. There is not a reasonable causal relationship between study drug administration and the AE.

11.4 Collection and follow up of Adverse Events

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

The adverse event-reporting period will be from participant consent until the participants final study 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 can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

All adverse events should be followed up until they are resolved or the participant's participation in the study ends (i.e. until the final CRF is completed for that participant). 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 even after the volunteer's participation in the study is over. Such events should be followed until resolution, or until no further change can reasonably be expected. Deaths occurring more than 30 days after the final dose, which are considered to be unrelated to the study medication, should not be reported as a Serious Adverse Event.

11.4.1 Serious Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence that at any dose:

i) Results in death

ii) Is life threatening

iii) Requires in-patient hospitalisation or prolongation of existing hospitalisation

iv) Results in persistent or significant disability/ incapacity

v) Is a congenital anomaly/ birth defect

OR

vi) Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See below for the definition of potential DILI).

Although pregnancy and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs (See pregnancy section below for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE.

11.4.2 Serious Adverse Event Collection and Reporting

Section 4.8 in the Summary of Product Characteristics (SmPC) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and up to 28 days after discontinuation of the study drugs. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

The SAE should be reported immediately to the Principal Investigator (within 24 hours of a member of the study team becoming aware of the event). A study SAE form should be completed, and an assessment of whether the SAE is a Suspected Unexpected Serious Adverse Reaction (SUSAR) conducted. The Principal Investigator is responsible for determining whether the SAE is a SUSAR and for reporting this in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements. Copies of both SAEs and SUSARs should also be sent to MSD within 24 hours of becoming aware of the event.

An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, and SUSARS whether related or not related to study drug, and pregnancies must be reported to the nominated person at the sponsor research and development office as set by the sponsor standard operating procedures (SOPs) within 24 hours of awareness of the event. Suspected Unexpected Serious Adverse Reactions (SUSARs) should also be notified to the marketing authorisation holder.

The assessment of expectedness should be made against the current version of the reference safety information.

11.4.3 Pregnancy

Any pregnancy, including pregnancies of partners of male participants, that occurs during study participation must be reported using the SAE form. To ensure subject safety, each pregnancy must be reported to the sponsor (see section 11.4.2) within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the sponsor, using the SAE form. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the sponsor (see section 11.4.2) where female study participants have been exposed to the IMP.

11.4.4 Other safety considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

12 Data handling

12.1 Recording of data

The data collected during the study will be recorded in an individual, participant specific Case Report Form (CRF). In order to maintain confidentiality, the participant will be identified only by participant codes on the CRF.

Any paper CRFs should be completed legibly in black ink by an appropriate member 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 signature log identifying personnel who can enter data and/or sign off a CRF will be maintained by the Principal Investigator.

Corrections to the data on paper CRFs will only be made by drawing a single line through the incorrect data (so as not to obscure the original entry) and inserting the correct data next to the original entry. The incorrect data must never be obliterated using correction fluid (e.g. Snopake® or Tippex®). Each correction will be initialled and dated by the person making the correction.

CRFs should be kept current to allow review and validation of data as required by the monitoring plan. CRFs will be completed, reviewed and signed off by the Investigator within two weeks of the last participant visit.

12.2 Source documentation and study records

The participant's number and date of entry into the study, along with a study identifier, should be recorded in the participant's study records. The following should also be recorded in the study records; confirmation of written and oral consent, the participant'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 and all study procedures at each visit.

12.3 Data management

Data will be entered into case report forms which may be paper or electronic. These will be used to generate the study database for analysis. The database will be kept in a secure location and access will be given to authorised personnel only, a log of which will be stored in the Trial Master File.

Any data anomalies or values found to be outside normal ranges will be checked with the Investigator. When corrections are required these will be made on CRF and the study database will be amended.

12.4 Archiving and storage of data

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

13 Quality control and quality assurance

13.1 Monitoring arrangements

The purpose of monitoring is to verify the rights and wellbeing of human participants 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 site visits for the purpose of monitoring various aspects of the study. The Investigator must agree to allow the study monitor to inspect all CRF and corresponding source documents, e.g. original medical records, participant 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.

A monitoring plan will be in place for this study in line with the relevant standard operating procedures of the sponsor.

13.2 Quality assurance

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 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.

14 Administrative procedures

14.1 Ethics approval

The study protocol, participant information and consent form, the Investigator Brochure, available safety information, participant recruitment procedures (e.g. advertisements), information about payments and compensation available to the participants and documentation evidencing the Investigator's qualifications should be submitted to the Ethics Committee for ethical review and approval according to local regulations, prior to the study start. Any changes, which may need to be made, will be submitted in the form of numbered and dated protocol amendments in accordance with local regulations.

14.2 Regulatory approval

As required by local regulations, approval of the appropriate regulatory bodies will be obtained, prior to study initiation.

14.3 Insurance provisions

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

14.4 Publication policy

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

14.5 Drug accountability

The investigator will ensure that the investigational product will only be used in accordance with the protocol.

Pifeltro® supplies will be kept in the hospital pharmacy in a secure, limited access storage area under the recommended storage conditions.

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 identification of the participant to whom the investigational product was dispensed, the date, the quantity, batch number and expiry date of the investigational product dispensed and the quantity of the investigational product unused/returned by the participant. These will be made available for review by the monitor as set out in the study monitoring plan and standard operating procedures.

Partially used or empty containers may be destroyed by pharmacy after completion of inventory and notification of and acknowledgement by sponsor research and development office. Due to the nature of the study and the need to dose participants outside of normal working hours, pharmacy may need to prepare and dispense investigational medicinal product to the unit in advance of Day 1. A process is in place to retrieve investigational medicinal product for those participants who are withdrawn after medication has been dispensed to the unit and prior to dosing. The dispensing may include additional contingency supply for Day 7 doses in case participants fail to bring back their Day 7 doses to the visit.

Due to the nature of the study and intensive pharmacokinetic days occurring outside normal working hour's pharmacy will dispense investigational medicinal product (IMP) to the unit. It is the responsibility of the investigator to release the IMP and to ensure that pharmacy is informed in order to document which participants received the IMP. Any IMP not required will be returned to pharmacy when no longer required for use in the study.

14.6 Sample shipment and processing

14.6.1 Safety analysis samples

All urinalysis will take place within the clinical research facility, samples may also be sent to one of the below labs in the event of a positive/abnormal result.

Biochemistry, haematology and virology samples will be analysed by the local hospital laboratories according to the local procedures.

Biochemistry & Haematology
Pathology Laboratory
Imperial College NHS Foundation Trust
Chelsea & Westminster Hospital
369 Fulham Road
London SW10 9TH

Virology & Hepatitis
Dept. of Infection & Immunity
9th Floor Laboratory Block
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

14.6.2 Pharmacokinetics analysis

PK samples will be processed by the HIV/GUM research laboratory and couriered to the following address for measurement of doravirine plasma concentrations:

Jefferies Research Trust Laboratories
Wright-Fleming Institute
Imperial College London
Dept. of Medicine, St Mary's Campus
Norfolk Place
London W2 1PG

14.6.3 Pharmacogenetics analysis

EDTA blood samples will be shipped to Liverpool with a coded label only, in dry ice, to the following address:

Professor Andrew Owen
Pharmacology Research Laboratories
Block H – First floor
70 Pembroke Place
Liverpool L69 3GF
Tel +44 (0) 151 794 5553
Fax +44 (0) 151 794 5656
Email: aowen@liv.ac.uk

14.6.4 Platelets/endothelium

Samples will be collected by a member of the specialised laboratory from the clinical research facility.

Dr Mike Emerson
Cardio-respiratory Interface Section
National Heart and Lung Institute
Imperial College London
SAF Building
London SW7 2AZ
Tel: +44 (0) 207 5941877
Email: m.emerson@imperial.ac.uk

14.6.5 Metabolomics

Plasma, urine and faecal samples will be processed as described in appendix 3 and stored at -80°C. Appropriate arrangements will be made for transport to laboratory for analysis.

Jefferies Research Trust Laboratories
Wright-Fleming Institute
Imperial College London
Dept. of Medicine, St Mary's Campus
Norfolk Place
London W2 1PG

15 References

1. Elliot ER, Cerrone M, Else L, Amara A, Bisdomini E, Khoo S, Owen A, Boffito M. Pharmacokinetics of dolutegravir with and without darunavir/cobicistat in healthy volunteers. J Antimicrob Chemother. 2019;74:149-156.

2. Wilby KJ, Eissa NA. Clinical Pharmacokinetics and Drug Interactions of Doravirine. Eur J Drug Metab Pharmacokinet. 2018;43:637-644.

3. https://www.medicines.org.uk/emc/product/9693/smpc

16 Appendices

Appendix 1: Study Flowchart

Appendix 2: DAIDS Grading Scale

Appendix 3: Collection, processing, shipping and storage of blood and plasma for pharmacokinetic analysis

Appendix 4: Highly effective methods for avoiding pregnancy in females of child bearing potential

Appendix 1: Study flowchart

	Screening visit	Baseline visit	Intensive PK visit[1]	PK TAIL[1]	FU/ETV
Time (days)	-28 to 0	1	7	8-10	20-23
Informed consent	X				
Demographic data	X				
Medical history/ concomitant disease	X				
Physical examination	X		X[8]		
Vital signs[10]	X	X	X		X
ECG	X				X[11]
Weight	X				
Height	X				
Urinalysis[2]	X	X	X		X[12]
HIV testing	X				
HBV & HCV testing	X				
Haematology[3]	X	X	X		X
Clinical chemistry[4]	X	X	X		X
Pharmacokinetics[5]			X		
24-72 hour Pharmacokinetics[5]				X	
Pharmacogenetics[6]		X[6]			
Metabolomics[7]		X	X		X
Platelet/endothelium blood sample		X	X		X
Adherence assessment[9]			X		X[12]
Witnessed dosing		X	X		
Adverse events		X	X		X
Start new drug		X			
Concomitant medication check	X	X	X		

[1] Patients will be admitted to the morning of the PK assessment days and will spend approximately 12 hours in the Unit.

[2] Urinalysis including macro-analysis, drug screen and pregnancy test (female subjects of child-bearing potential)

[3] FBC (Hb, WBC, platelets, RBC, MCV, MCH, MCHC, RDW, HCT/PCV and MPV) with a differential and clotting screen

[4] Fasting (except for screening visit) for at least 8 hours and including U&Es (creatinine, urea, potassium, sodium, chloride, estimated GFR, bicarbonate), LFTs (bilirubin, ALT, alkaline phosphatase, albumin, AST, GGT), Bone Profile (calcium, calcium adjusted, phosphate, total protein, albumin, globulin), glucose, amylase, Lipids (total cholesterol, triglycerides, HDL, LDL)

[5] Subjects will undergo 3 PK assessment days in total. Blood will be drawn over the full dosing interval at the following time-points: pre dose (within 10 minutes before dosing), 2, 4, 8, 12, 24, 30, 36, 48, 54, 60, 72 hours post dose (+/- 10min).

[6] This sample can be collected on Day 1 or any other study day for those subjects who consent

[7] See appendix 3 for details of metabolomics samples

[8] Only if clinically indicated

[9] Including pill count on Day 7

[10] Temperature, Blood Pressure, Heart Rate and Respiratory Rate

[11] ECG at ETV visit only

[12] At ETV visit only if required

ETV= Early termination visit (subjects will not be required to attend for follow up visit) FU= Follow Up visit (required for subjects that have completed all study visits)

Appendix 2: DAIDS grading scale

Please reference latest version of grading scale available at below location.

https://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf

Appendix 3: Collecting, processing, shipping and storing of blood, plasma, urine and faeces for pharmacokinetics (PK), pharmacogenetics (PG), metabolomics and platelet/endothelium markers.

A) Pharmacokinetic analysis

At each scheduled blood draw, approximately 12 mL of whole blood will be collected from an in-dwelling venous catheter or by direct venepuncture into two Vacutainer® blood collection tube (Lithium heparin). If saline flushes are used to keep the peripheral catheter functional then a small volume of blood (1 mL) should be withdrawn from the catheter before sample collection and discarded.

Immediately after collection, the blood tube will be inverted several times and kept on wet ice or refrigerated as well as protected from light until centrifugation. Within 90 minutes of blood collection each blood sample will be centrifuged in a refrigerated clinical centrifuge for 10 minutes at 2000 g at 4°C. Plasma will then be transferred and aliquoted equally into three opaque polypropylene storage tubes with caps.

Each tube must be appropriately labelled and stored at -20°C or lower. One tube must be kept for back-up and two tubes will be transferred by courier to:

Jefferies Research Trust Laboratories
Wright-Fleming Institute
Imperial College London
Dept. of Medicine, St Mary's Campus
Norfolk Place
London W2 1PG

B) Pharmacogenetic analysis

Full blood will be collected in a 4 mL EDTA tube. The label will report only a coded identification number. The samples will be stored at -20°C until transferred by courier in dry ice to:

Professor Andrew Owen
Pharmacology Research Laboratories
University of Liverpool
Block H – First floor
70 Pembroke Place
Liverpool L69 3GF

Tel. +44 (0) 151 794 5553
Fax. +44 (0) 151 794 5656
Email aowen@liv.ac.uk

C) Platelet aggregation/endothelium markers sampling

3 x 4.5mL citrate vials will be handed to a member of the specialised laboratory to be analysed in an aggregometer and flow cytometer.

Samples will be collected: on Day 1 pre-dose; on Day 7 post-dose and at FU visit.

Dr Michael Emerson
National Heart and Lung Institute
Sir Alexander Fleming Building
Imperial College London
London SW7 2AZ

D) Metabolomics sampling

Plasma samples

At each scheduled blood draw, approximately 12 mL of whole blood will be collected from an in-dwelling venous catheter or by direct venepuncture into two Vacutainer® blood collection tube (EDTA). If saline flushes are used to keep the peripheral catheter functional then a small volume of blood (1 mL) should be withdrawn from the catheter before sample collection and discarded. Immediately after collection, the blood tube will be inverted several times and kept on wet ice or refrigerated as well as protected from light until centrifugation. Within 90 minutes of blood collection each blood sample will be centrifuged in a refrigerated clinical centrifuge for 10 minutes at 2000 g at 4°C. Plasma will then be transferred and aliquoted (500 µL/aliquote) equally into six opaque polypropylene storage tubes with caps (Five for analysis and one for back-up). Each tube must be appropriately labelled and stored at -80°C.

Urine samples

Midstream of urine (approximately 10 mL) will be collected using 50ml Falcon tube (FalcomTM) and kept on ice once patients hand over the samples. Within 30 minutes of urine collection, each urine sample will be centrifuged in a refrigerated clinical centrifuge for 10 minutes at 2000g at 4°C. Supernatant will then be transferred and aliquoted (500 µL/aliquote) into six opaque polypropylene storage tubes with caps (Five for analysis and one for back-up). Care should be taken not to disturb the bottom of the tube whether there is a visible pellet or not. Samples and tubes will be kept on ice during processing. Each tube must be appropriately labelled and stored at -80°C.

Faecal samples

Participants will be given faeces containers (Sarstedt 101x16.5mm) with short special spoon to collect a defined faeces sample and stool sample collection device (HYSTOOL®). Participants will be instructed to sample three aliquots at distinct topographical locations of the faecal sample and place each aliquot into an individual faeces container. The subjects will be asked to place samples immediately in a home freezer and return to them to the unit in a provided cold pack and bag. Each container should be labelled with time of collection. The faecal sample should be collected closest to the time of visits (less than 24 hours) and given to clinical staff at the time of visit. The containers will be stored at -80°C. As an alternative to freezing samples the protocol allows tubes to be provided to participants with a 95% ethanol solution to preserve the sample. It should be clearly recorded which option was used.

Appropriate arrangements will be made for transport to laboratory for analysis:

Jefferies Research Trust Laboratories
Wright-Fleming Institute
Imperial College London
Dept. of Medicine, St Mary's Campus
Norfolk Place
London W2 1PG

Appendix 4: 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 FCBP with same sex partners, when this is their preferred and usual lifestyle.

- Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle [Hatcher, 2007a]
- Oral contraceptive, either combined or progestogen alone [Hatcher, 2007a] plus male condom
- Injectable progestogen [Hatcher, 2007a] plus male condom
- Implants of etonogestrel or levonorgestrel [Hatcher, 2007a] plus male condom
- Estrogenic vaginal ring [Hatcher, 2007a] plus male condom
- Percutaneous contraceptive patches [Hatcher, 2007a] plus male condom
- Intrauterine device or intrauterine system that meets the effectiveness criteria as stated in the product label [Hatcher, 2007a]

- Hormone-free Intrauterine device that meets the effectiveness criteria as stated in the product label [Hatcher, 2007a]
- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a]. The information on the male sterility can come from the site personnel's: review of subject's medical records; medical examination of the subject and/or semen analysis; or interview with the subject on his medical history.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide[a] (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

[a] Nonoxynol-9 is the critical component in most spermicides, and is regarded as an acceptable spermicidal agent. Concern has been raised that nonoxynol-9 damages the epithelial lining of the vagina, and exposure may facilitate transmission of viruses, particularly HIV. The World Health Organization conducted a technical consultation in October 2001 and concluded that the increased risk for such transmission was low to minimal [WHO/CONRAD, 2003].

* A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH**) level > 40mIU/mL to confirm menopause.

** Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level.