PRODUCT: MK-1439/MK-1439A	PROTOCOL/AMENDMENT VERSION NO.: 1.0
REVOPS ID NO: NIS101573 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08052.003	CORE DRC APPROVAL DATE: 28-JUL-2022

PASS INFORMATION

Title	Post-marketing study to assess the effectiveness of doravirine-included in highly active antiretroviral therapy (HAART) in HIV-1 infected adult Chinese patients
Protocol Version identifier	MK1439-088/Version 1.0
Date of last version of protocol	Not applicable
EU PAS Register No:	Study not registered
Active substance	Doravirine tablets (PIFELTRO™):100 mg of doravirine Doravirine, lamivudine, and tenofovir disoproxil fumarate tablets (DELSTRIGO™): 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate
Medicinal product(s):	PIFELTRO™(MK-1439) and DELSTRIGO™ (MK-1439A)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s) (MAH)	Merck Sharp & Dohme LLC 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065 USA.
Joint PASS	No
Research question and objectives	The objective of this non-interventional study is to assess the effectiveness of doravirine-included HAART in HIV-1 infected adult Chinese patients.
Country(-ies) of study	China

PRODUCT: MK-1439/MK-1439A	PROTOCOL/AMENDMENT VERSION NO.: 1.0
REVOPS ID NO: NIS101573 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08052.003	CORE DRC APPROVAL DATE: 28-JUL-2022

Author	PPD Associate Principal Scientist, Biostatistical and Research Decision Sciences (BARDS) Epidemiology, Merck Sharp & Dohme LLC PPD
Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme LLC. 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065 USA.
Merck Final Repository (REDS) Date	12-SEP-2022
Date of Health Authority Approval of Protocol	Not applicable

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
cART	Combination Antiretroviral Therapy
[redacted]	
CRF	Case report form
DAA	Direct Acting Antivirals
DOR/3TC/TDF	Doravirine/lamivudine/tenofovir disoproxil fumarate
EMR	Electronic Medical Record
ERC	Ethics Review Committee
FI	Fusion Inhibitor
GPP	Good Pharmacoepidemiology Practice
HAART	Highly Active Antiretroviral Therapy
HGRAC	Human Genetic Resource Administration of China
HIS	Hospital Information System
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
IRB	Institutional Review Board
INSTI	Integrase Strand Transfer Inhibitor
LIS	Laboratory Information System
NMPA	National Medical Products Administration
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRDL	National Reimbursement Drug List
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SQI	Significant Quality Issue
VL	Viral Load
VS	Virologic Suppression

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LIST OF DEFINITIONS

Index Date	The date of the first treatment of PIFELTRO™ or DELSTRIGO™
Baseline	Time window prior to the index date during which baseline characteristics are being collected
ART Naïve Patients	No documented use of ART at any time prior to index date
ART Experienced Patients	Has documented use of ART at any time prior to index date
Virologic Suppression	Plasma HIV-1 RNA less than 50 copies per mL at week 48±8 following PIFELTRO™ or DELSTRIGO™ treatment.
Virologic Failure	Continuous plasma HIV RNA viral load of >200 copies/mL after 24 weeks of treatment (initiation or switch), or detectable viral load of ⩾200 copies/mL after achieving virologic suppression
Discontinuation	A ⩾60-day gap for PIFELTRO™ or DELSTRIGO™

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1 RESPONSIBLE PARTIES

Principal investigator	PPD Beijing You An Hospital, Capital Medical University, China
Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD MSD R&D (China) Co., Ltd.
Other contacts	PPD MSD R&D (China) Co., Ltd.
Supplier/Collaborator	PPD
Investigators	To be determined
Shared responsibilities	Not applicable

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REVOPS ID NO: NIS101573 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08052.003	CORE DRC APPROVAL DATE: 28-JUL-2022

2 ABSTRACT

Title	Post-marketing study to assess the effectiveness of doravirine-included in highly active antiretroviral therapy (HAART) in HIV-1 infected adult Chinese patients
Protocol Number / Version	MK1439-088/Version 1.0
Date	Not applicable
Author	PPD, MSD R&D (China) Co., Ltd
Rationale & Background	PIFELTRO™(MK-1439) and DELSTRIGO™(MK-1439A) were approved in China in November and December 2020 respectively. [redacted]
Research Question(s) & Objective(s)	Primary objective: to assess the effectiveness of doravirine-included HAART in HIV-1 infected adult Chinese patients; Secondary objective: to describe demographic, clinical characteristics, and treatment patterns of study population
Study Design	A retrospective multicenter observational study using medical chart review.
Population	HIV-I infected adult Chinese patients receiving doravirine-included HAART treatment.
Variables	Exposure: PIFELTRO™ and DELSTRIGO™ treatment Primary outcome: virologic suppression (VS, HIV-1 RNA< 50 copies/mL) achieved at week 48±8 following PIFELTRO™ and DELSTRIGO™ administration Secondary outcomes: HIV-1 treatment patterns

Data Sources	Relevant patient-level information will be collected from multiple information systems, including the Electronic Medical Record (EMR)/paper medical records, Hospital Information System (HIS), Laboratory Information System (LIS), and routine patient management material from clinicians in selected hospitals. The databases contain both inpatient and outpatient data. Data will be collected with the use of a standardized case report form.
Study Size	Approximately 210 patients will be evaluated. About 350 patients will be included with an estimated evaluability rate of 60%. Assuming 60%~90% of patients are virally suppressed at week 48±8, the width of 95% confidence interval (CI) will range from 13.2% to 8.2%.
Data Analysis	A descriptive analysis will be conducted. For the continuous variables: • Mean/median, standard deviation (SD), min/max • Interquartile range (IQR, including the first quartile [Q1] and third quartile [Q3]) For categorical variables: • Frequency and percentages Statistical comparisons will be conducted using chi-square test for categorical variables and Student's t-test, Mann-Whitney U test, Kruskal-Wallis H test for continuous variables as appropriate. Effectiveness will be assessed as the proportion of patients with VS at week 48±8 will be calculated with a 95% CI. It will be stratified by patient subgroups based on exposure to antiretroviral therapy (ART) medications at the time of PIFELTRO™ or DELSTRIGO™ initiation if applicable.

Milestones	
Start of data collection:	Start date of data collection will be a date (planned Jul 2023) after Human Genetic Resource Administration of China (HGRAC) approval
End of data collection:	Apr 2024
Interim report(s) of study results:	Not applicable
Study progress report(s):	Not applicable
Final report of study results:	Nov 2024 [redacted]

3 AMENDMENTS AND UPDATES

Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
Not applicable						

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4 MILESTONES

Milestone	**Planned Date**
<Registration in the EU PAS register>	Within 35 days of protocol finalization in Regulatory Enterprise Document Source (REDS)
Start of data collection	Start date of data collection will be a date (planned Jul 2023) after Human Genetic Resource Administration of China (HGRAC) approval
End of data collection	Apr 2024
Final report of study results	Nov 2024 [redacted]

5 RATIONALE AND BACKGROUND

Human immunodeficiency virus (HIV) is the etiologic agent of acquired immunodeficiency syndrome (AIDS). Ongoing infection with HIV remains a serious challenge to health. If left untreated, HIV targets the immune system by depletion of $CD4^+$ T cells, leading ultimately to AIDS, opportunistic infections, and death. In 2020, the global burden of HIV/AIDS was 37.7 million cases, corresponding to 0.5% of the world's population, and the total number of new infections and AIDS-related deaths was 1.5 million and 0.68 million, respectively [Joint United Nations Programme on HIV/AIDS 2022].

The HIV infection (mainly HIV-1 infection) epidemic in China has evolved significantly over the past 35 years and it remains a major public health problem. The number of newly diagnosed cases has increased each year from 41 thousand in 2004 to 135 thousand in 2017. At the end of 2020, there were 1.053 million people living with HIV and 351,000 cumulative reported deaths in China [He, N. 2021].

The use of combination antiretroviral therapy (cART) prevents the depletion of $CD4^+$ T cells, resulting in restoration of the immune system. cART has changed HIV infection from a fatal illness to a chronic disease. At the end of 2020, 978,138 (92.9%) out of the total of 1.053 million PLWH in China were receiving antiretroviral therapy (ART), 96.1% of those on ART were able to achieve virologic suppression [He, N. 2021].

Currently, there are more than 30 individual drugs and fixed-dose combinations available for the treatment of HIV infection. These agents belong to six distinct mechanistic classes known as reverse transcriptase inhibitors (nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs]), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (CCR5 co–receptor antagonists), and integrase strand transfer inhibitors (INSTIs).

Updated Chinese guidelines for diagnosis and treatment of HIV/AIDS (2021 edition) recommend initiating ART in treatment naïve patients with a regimen consisting of two NRTIs along with a third antiretroviral agent from NNRTI class, PI class or INSTI class, while single-tablet regimen offers patients with additional options [AIDS and Hepatitis C Professional Group, Society of Infectious Diseases, Chinese Medical Association 2021]. The recommendations from the IAS–USA Antiretro-viral Guidelines on initial antiretroviral regimens, including an INSTI plus 2 NRTIs, or NNRTI/ boosted PI plus 2 NRTIs [Volberding, P. A. 2017].

Doravirine (DOR, tradename PIFELTRO™) is an NNRTI that is indicated in combination with other antiretroviral medicinal products for the treatment of adults infected with HIV-1 without resistance to the NNRTI class. Doravirine, lamivudine, tenofovir disoproxil fumarate (DOR/3TC/TDF, tradename DELSTRIGO™) is a fixed-dose combination indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine and tenofovir. As one of the highly efficacious and well tolerated NNRTIs, active against both wild type virus and most common NNRTI resistant variants at

concentrations achieved with once daily dosing, PIFELTRO™ and DELSTRIGO™ have been approved in more than 50 countries, such as the US, EU, Canada, Switzerland, Australia, etc. PIFELTRO™ and DELSTRIGO™ were approved in China in 24-Nov-2020 and 29-Dec-2020, respectively.

PIFELTRO™ can be taken without regard to food and has a low potential for drug–drug interactions, including with acid-reducing drugs. In the randomized, controlled, double-blind, multicenter, non-inferiority, phase-3 trial conducted at 125 clinical centers in 15 countries (DRIVE-FORWARD), 769 participants were randomly assigned to treatment (385 with PIFELTRO™ and 384 with ritonavir-boosted darunavir), with two investigator-selected NRTIs. At week 48, 321 (84%) antiretroviral-naïve participants in the PIFELTRO™ group and 306 (80%) in the darunavir group achieved plasma HIV-1 RNA of less than 50 copies per mL (difference 3.9%, 95% CI –1.6 to 9.4), indicating non-inferiority of the doravirine-containing regimens to ritonavir-boosted darunavir-containing regimens. The change in CD4+ T cell counts from baseline to week 48 was also similar in the two treatment groups. PIFELTRO™ was generally well tolerated up to 48 weeks of treatment [Molina, J. M., et al 2018]. At week 96, a higher proportion of the PIFELTRO™ group (277 [73%] of 383) achieved an HIV-1 RNA concentration of less than 50 copies per mL than did those in the darunavir group (248 [66%] of 383; difference 7·1%, 95% CI 0. 5–13.7) [Molina, J. M., et al 2020]. In another phase 3, double-blind, non-inferiority trial at 126 sites worldwide (DRIVE-AHEAD), antiretroviral treatment–naive adults with ≥1000 HIV-1 RNA copies/mL were randomized (1:1) to either DELSTRIGO™ or EFV/FTC/TDF. At week 48, 84.3% (307/364) of DELSTRIGO™ recipients and 80.8% (294/364) of EFV/FTC/TDF recipients achieved <50 HIV-1 RNA copies/mL (difference 3.5%, 95% CI, -2.0, 9.0), which demonstrated non-inferior efficacy of DELSTRIGO™ to EFV/FTC/TDF [Orkin, C., et al 2019]. The efficacy of switching from a baseline regimen (consisting of two NRTIs in combination with a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or an NNRTI) to DELSTRIGO was evaluated in a randomized, open-label trial (DRIVE-SHIFT). Subjects must have been virologically suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen for at least 6 months prior to trial entry, with no history of virologic failure. Subjects were randomized to either switch to DELSTRIGO at baseline, or stay on their baseline regimen until Week 24, at which point they switched to DELSTRIGO. At week 48, 90.8% (406/447) on DOR/3TC/TDF had HIV-1 RNA ＜50 copies/mL, demonstrating noninferiority vs Baseline Regimen at week 24 [difference -3.8 (-7.9 to 0.3)]. Of the 209 participants in the Baseline Regimen who switched to DOR/3TC/TDF at week 24, 198 (94.7%) had HIV-1 RNA ＜50 copies/mL at week 48 [Johnson, M., et al 2019].

5.1 Rationale

PIFELTRO™ and DELSTRIGO™ were approved in China on 24-Nov-2020 and 29-Dec-2020 separately. [redacted]

[redacted] conduct a retrospective multicenter observational study to assess the effectiveness of doravirine-included highly active antiretroviral therapy (HAART) in HIV-1 infected adult Chinese patients. People infected with HIV/AIDS go to a local designated hospital to access ART and other treatments in China. Therefore, the HIV treatment mode presents the feature of patient accumulation in the designated hospital. Patients are more likely to be retained in care at the hospital where they initiate treatment. Based on the preliminary assessment of the potential number of patients prescribed doravirine-included HAART in several infectious disease hospitals, as well as the medical treatment mode mentioned above, it is feasible to conduct a retrospective observational study with these designated hospitals as study sites. In addition, the retrospective observational study design will help to get the effectiveness data of the product in Chinese patients as early as possible.

Another advantage of the observational study using medical chart review is that the effectiveness study can be conducted without any intervention, which will obtain information on patients receiving doravirine-included HAART to better reflect real-world clinical practice. It is the most feasible way to take electronic medical records as the basic data source in research methods. [redacted]

6 RESEACH QUESTION AND OBJECTIVES

The aim of this study is to assess the effectiveness of doravirine-included HAART in HIV-1 infected adult Chinese patients by a retrospective observational study design using medical chart review.

6.1 Primary Objectives

To assess the effectiveness of doravirine-included HAART in HIV-1 infected adult Chinese patients. The effectiveness will be evaluated at week 48±8 among patients who have data available to confirm the achievement of virologic suppression (VS, defined as plasma HIV-1 RNA less than 50 copies per mL at week 48±8) after 48±8 weeks' treatment of PIFELTRO™ or DELSTRIGO™.

6.2 Secondary Objectives

Among HIV-1 infected adult Chinese patients who has been treated with PIFELTRO™ or DELSTRIGO™:

To describe demographic and clinical characteristics, including:

- Demographic characteristics at baseline;
- Clinical characteristics including medical history, diagnosis history and VL, specifically the;

- Medical history including comorbidities and concomitant medications on index date* and during the 48±8 weeks observation period;
- Diagnosis history including date of HIV diagnosis and patient type receiving cART;
- Viral load (HIV-1 RNA) at key time points, including baseline period, week 48±8 and any follow-up visits during the observation period.

To describe HIV-1 treatment patterns among the study population, including:

- cART regimens during the 1-year prior to index date and the 48±8 weeks observation period;
- Discontinuation of PIFELTRO™ or DELSTRIGO™ treatment during the 48±8 weeks observation period.

*: Refer to 7.2.3.4 for definition.

7 RESEARCH METHODS

7.1 Study Design

The study does not involve any interventional measurements, e.g., receiving oral doravirine, laboratory test for $CD4^+$ T cell count and viral load. Under this protocol, all patients accepted ART previously in the course of routine clinical practice.

The design is a retrospective multicenter observational study using medical chart review. Adult HIV-1 infected patient (>=18 years old) who has been treated by PIFELTRO™ or DELSTRIGO™ in accordance with National Medical Products Administration (NMPA)'s approved product information are potential subjects for the study. After inclusion/exclusion criteria check, the patients who have continued PIFELTRO™ or DELSTRIGO™ for 48±8 weeks and have VL data at 48±8 weeks will be evaluated, and all the information will be collected through retrospective medical chart review including but not limited to outpatient or inpatient medical records, lab reports, prescription records, etc., by qualified investigators.

Effectiveness will be evaluated as the proportion of patients achieving VS who continued PIFELTRO™ or DELSTRIGO™ for 48±8 weeks and have VL data at 48±8 weeks. The proportion will be calculated as the number of patients achieving VS at week 48±8 divided by the number of patients who have VL data at 48±8 weeks [will include patients with VS and virologic failure (defined as continuous plasma viral load of ＞200 copies/mL after 24 weeks of treatment, or detectable viral load of ≥200 copies/mL after achieving virologic suppression)].

The demographic, clinical characteristics and HIV-1 treatment patterns will be described in this study.

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7.2 Setting

7.2.1 Study Population

The study population will consist of HIV-1 infected adult patients receiving doravirine-included HAART treatment. The patients who meet all the inclusion criteria and fail to meet any exclusion criterion will be included in the study.

- **Inclusion criteria**
  - Chinese and resident in China, i.e., Chinese descent born in China, and have a Chinese home address
  - New users of PIFELTRO™ or DELSTRIGO™
  - At least 18 years of age on the day of initiating PIFELTRO™ or DELSTRIGO™
- **Exclusion criteria**
  - Off-label treatment with PIFELTRO™ or DELSTRIGO™ (as approved in China), including the following criteria:
    1) Pregnancy on index date, or breast-feeding on index date
    2) For those patients treated with DELSTRIGO™, documented CrCl <50 mL/min on index date
    3) For those patients treated with PIFELTRO™ or DELSTRIGO™, documented end-stage renal disease, undergoing dialysis or severe hepatic impairment (Child-Pugh Class C) on index date
  - Participating in any clinical trial (interventional)
  - Has documented or known resistance to NNRTIs and other drugs included in ART prior to initiation of PIFELTRO™ or DELSTRIGO™
  - There is a written reason of doravirine-included HAART termination due to the national reimbursement drug list (NRDL) adjustment in China in the early 2022

7.2.2 Study Sites

The hospitals in which PIFELTRO™ or DELSTRIGO™ are available since August 2021 (the earliest month recorded for PIFELTRO™ or DELSTRIGO™ prescription) and have the most patients using these two products during the study period will be considered.

Site selection will depend on the potential eligible patient number, willingness of PI to participate, the completeness of medical records on study key information as well as the

feasibility assessment from the operational perspective. Currently PIFELTRO™ or DELSTRIGO™ are not included into NRDL thus the projected sale volume is expected to be small due to high coverage of free HAART drugs and competition from other products. According to the marketing investigation, majority of these two drugs will be prescribed in 8-10 designated hospitals for HIV infected patients. Thus about 8 sites will be selected for the study. The actual site numbers may be updated according to the actual execution.

The study key information should include but not limited to study-related demographic, clinical (including medical history, diagnosis history and VL) and treatment information (including cART regimens and discontinuation).

7.2.3 Study Period

Figure 1 depicts the study period. The study period may be adjusted according to the actual enrollment of patients with available data to confirm the achievement of VS at week 48±8.

7.2.3.1 The Patients Accrual Period

The accrual period is the segment of time in which patients are admitted to the hospital and receive treatment of PIFELTRO™ or DELSTRIGO™. It will last for about 1.5 years starting from August 2021 to March 2023. In principle, the patients who take the first tablet of PIFELTRO™ or DELSTRIGO™ exceed March 2023 will not be followed and observed [redacted]

7.2.3.2 The Observation Period

For each patient, it is defined as from the day of first tablet of PIFELTRO™ or DELSTRIGO™ administration (Index date, see 7.2.3.4) until 48±8 weeks' treatment, discontinuation of PIFELTRO™ or DELSTRIGO™, or death, within a study period of August 2021 to January 2024 (the time of the last patient enrolled completes 48±8 weeks' treatment)

7.2.3.3 The Data Extraction Period

Data extraction will initiate once the site has accumulated target number of patients who have available data to confirm the achievement of VS at week 48±8. Start date will be a date after Human Genetic Resource Administration of China (HGRAC) approval. It is estimated that data extraction will be from July 2023 to March 2024. Starting date for the last site is no later than January 2024 [redacted]

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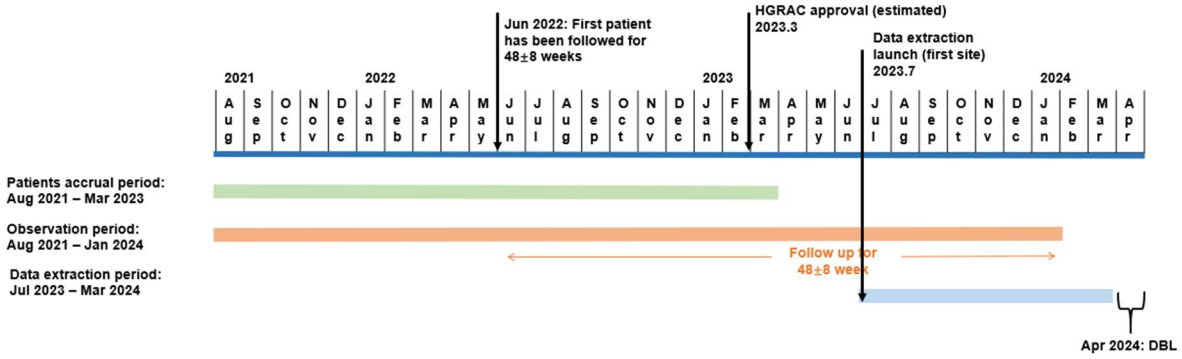

Figure 1 Patients Accrual, Observation and Data Extraction Period in the Present Study

7.2.3.4 Index date and specific time periods

Index date is defined as the date of the first treatment of PIFELTRO™ or DELSTRIGO™.

Specific time periods for different measures in the data extraction process are summarized as follows:

- For resistance to NNRTIs and other drugs: prior to index date and the 48±8 weeks observation period
- For cART regimens: within 1 year prior to index date and the 48±8 weeks observation period
- For viral load: within 30 days prior to index date (baseline period to establish VL), at week 48±8 and any time during the observation period
- For comorbidities, concomitant medications and discontinuation: during the observational period
- For CrCl: within 30 days prior to index date
- For breast-feeding: within 30 days prior to index date and during the observation period.
- For end-stage renal disease, undergoing dialysis and severe hepatic impairment (Child-Pugh Class C): within 180 days prior to index date.
- For pregnancy: within 1 year prior to index date and during the observation period.

7.3 Variables

7.3.1 Exposure

The study exposure of interest is PIFELTRO™ or DELSTRIGO™ treatment. However, this study does not involve the active PIFELTRO™ or DELSTRIGO™ treatment. The study will include patients who received PIFELTRO™ or DELSTRIGO™ treatment in routine clinical practice.

If applicable, patients will be assessed among the following sub-groups based on their exposure to ART based on any available data, which may include: prescription documented in medical record, pharmacy claims, dispensing records, et al:

- ART Naïve Adults
- ART Experienced Adults with or without virologic suppression

7.3.2 Outcomes

7.3.2.1 Primary Outcomes

The primary outcome is VS achieved at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration.

Laboratory measurements of HIV-1 RNA testing will be extracted from the chart review of the medical records. Only quantitive viral load (HIV-1 RNA) measurement or qualitative measurement with a limit of 50 copies/mL or lower (e.g., <40 copies/mL or <20 copies/mL) will be used to determine the VS.

Patients with continuous use of PIFELTRO™ or DELSTRIGO™ during the observation period will be included in the VS calculation. This will include patients with virologic failure before week 40 (The virologic failure is designated by investigators and documented in EMR/paper medical records), but those who meet the definition of treatment discontinuation (evidence of ⩾60 day gap in treatment, see 7.3.2.2.2) will not be included in the assessment.

7.3.2.2 Secondary Outcomes

In support of the secondary objectives, we will report the following patient demographic, clinical characteristics and HIV-1 treatment patterns in the study population. Pending data availability, related variables may be adjusted and will be finalized in the case report form (CRF).

7.3.2.2.1 Demographic and Clinical Characteristics

Demographic Variables at Baseline

- Year and month of birth
- Age
- Gender
- Height and weight
- Smoking
- Alcohol use
- Geographic region (e.g., rural/urban, eastern/middle/western)
- Type of medical insurance
- Insurance coverage for PIFELTRO™ or DELSTRIGO™

Clinical Variables

Medical History

- Comorbidities
- Presence of concomitant medications (e.g., hepatitis drugs [direct acting antivirals (DAA)], calcium supplements, rifabutin, dabrafenib)

Diagnosis History

- Date of HIV-1 diagnosis
- Patient type receiving cART (naïve/experienced)
- Pregnancy (yes/no)
- Breast-feeding (yes/no)
- Death date

Laboratory Measures (Viral Load)

For each testing result:

- Testing date of HIV-1 RNA viral load
- Lab testing methods at local laboratory for HIV-1 RNA including reverse transcription polymerase chain reaction (RT-PCR), NASBA or real-time Polymerase Chain Reaction (PCR) (e.g., Abbott Real-time HIV-1 assay)
- Viral load within 30 days prior to index date, at week 48±8 and any time during the observation period
- Qualitative measurement of viral load (if applicable)

7.3.2.2.2 HIV-1 Treatment Patterns

cART Regimen Related Variables

- Class of ARTs prior to PIFELTRO™ or DELSTRIGO™ administration
- Description of all previous ARTs in experienced patients (including anchor agent class [including NNRTIs, PIs, INSTIs or fusion inhibitor], background NRTIs, pill burden [e.g., single tablet regimen, multiple tablet regimen])
- Evidence on the resistance to NNRTIs prior to PIFELTRO™ or DELSTRIGO™ administration
- Evidence on the resistance to other drugs included in HAART except NNRTIs prior to PIFELTRO™ or DELSTRIGO™ administration
- Description of doravirine based regimen (including background NRTIs, pill burden [e.g., single tablet regimen, multiple tablet regimen])
- Evidence of PIFELTRO™ or DELSTRIGO™ prescription (e.g., date of prescription, dosing instructions, prescription duration)

Discontinuation of PIFELTRO™ or DELSTRIGO™ Treatment (if applicable)

- PIFELTRO™ or DELSTRIGO™ discontinuation (yes/no)
- Stop date of PIFELTRO™ or DELSTRIGO™ treatment (date when previously dispensed medications were expected to be finished or documented by the clinician in medical records)
- Viral load at discontinuation

A ⩾60-day gap for PIFELTRO™ or DELSTRIGO™ is considered as discontinuation of treatment. Patients who restarted PIFELTRO™ or DELSTRIGO™ treatment after a ⩾60-day gap remained classified as discontinued. It will be identified as documented by the clinician in medical records or calculated as a minimum 60-day gap between the prescription refill date and the date when previously dispensed medications were expected to be finished. A change in backbone alone will not constitute discontinuation.

When a patient was considered to have discontinuated PIFELTRO™ or DELSTRIGO™ treatment, the below categories will be classified as the reason for discontinuation, if applicable:

- Prior treatment failure (including resistance, viral loads ⩾200, etc.)
- Drug-drug interactions (e.g., potential, actual)
- Tolerability
- Financial (e.g., insurance coverage)
- Simplification
- Pregnancy
- Others (cannot be free text)
- Not documented

7.3.3 Covariates

Due to the retrospective chart review design, it is unlikely to access each patient's data of prescribed medication for the entire period since the index date in the hospitals in China. Thus adherence will not be considered when calculating the effectiveness endpoint. However, adherence will be used in sub-group analysis to investigate whether using the adherence would lead to a difference in effectiveness results, if data are available.

7.3.3.1 Adherence

7.3.3.1.1 Calculation of Adherence

Adherence will be assessed for 48±8 weeks periods, which is calculated as the pills they have been prescribed divided by the total pills they should be prescribed over the whole period [Puskas, C. M., et al 2017]. Specifically, for the time interval between the last prescription and HIV viral load testing, the pills prescribed should be regarded as been taken by patients and added in the numerator.

Adherence will be only calculated for DOR in the regimen or DELSTRIGO™.

7.3.3.1.2 Medication Variables

The following medication variables will be recorded for each patient between index date until week 48±8 following PIFELTRO™ or DELSTRIGO™ treatment, discontinuation or death before week 48±8:

- Date of prescription
- Prescription dose
- Dosing instructions
- Duration between the two prescriptions (days)
- Prescriber

7.4 Data Sources

Relevant patient-level information will be collected from multiple information systems, including EMR/paper medical records, Hospital Information System (HIS, mainly providing prescription information), Laboratory Information System (LIS), and routine patient management material from clinicians (mainly providing refill information) in selected hospitals. The databases contain both inpatient and outpatient data. Data will be collected with the use of a standardized case report form.

7.4.1 Study Procedures

General Procedure

This study does not involve active administration of PIFELTRO™ or DELSTRIGO™. The study protocol will be submitted for approval by the institutional review board (IRB)/ethics review committee (ERC).

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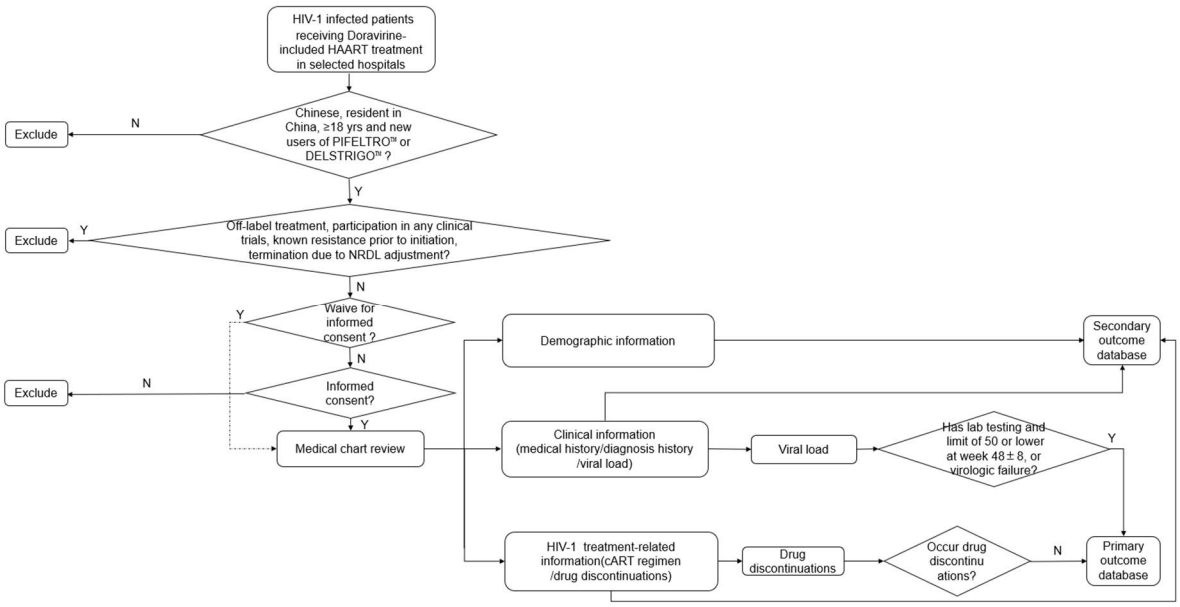

Figure 2 Procedures of Eligible Patients Enrollment and Data Generation

The Data Collection Procedure

Given that the study is a retrospective medical chart review, the participating practitioner will submit the study to the IRB/ERC to let IRB/ERC determine whether the study qualifies to waive for informed consent.

Medical chart review will initiate in selected hospitals once the site has accumulated target number of patients who have available data to confirm the achievement of VS at 48±8 weeks. The chart review will initiate in July 2023 (estimated based on HGRAC approval date) until the overall study enrollment goal is achieved, no matter how many patients for each site has been accrued. With the use of a standardized case report form, demographics, clinical and treatment information will be extracted from medical charts by trained staff.

7.5 Study Size

Approximately 210 patients will be evaluated. About 350 patients will be included with an estimated evaluability rate of 60%. Assuming 60% ~ 90% of patients achieving VS at week 48±8, the width of 95% CI will range from 13.2% to 8.2%. Table 1 shows the width of 95% CI for this sample size.

Due to the impact of NRDL adjustment in the early 2022, the number of patients on Doravirine who have viral load endpoints at 48±8 weeks in HIV-1 infected adult Chinese patients in selected site hospitals is not currently known and is for primary objective of this study. Thus, this may allow final analysis with smaller sample size than 210 patients to be evaluated [redacted]

Table 1 Sample Size Calculation for the Effectiveness Study of Doravirine-Included HAART

Proportion of patients achieving VS	95% Confidence Interval	Width
60%	53.4%-66.6%	13.2%
70%	63.8%-76.2%	12.4%
75%	69.1%-80.9%	11.8%
80%	74.6%-85.4%	10.8%
85%	80.2%-89.8%	9.6%
90%	85.9%-94.1%	8.2%

7.6 Data Management

All data management activities including data capture, data storage, data cleaning, data security, and system backup processes will be undertaken by qualified personnel and will follow all procedures detailed in a separate “Data Management Plan”.

In this study, data management activities include, but are not limited to security, programming, systems and data validation, sequencing of operational steps and events, quality assurance and data backup. These procedures are intended to ensure the authenticity, integrity, and confidentiality of electronic records.The study will comply with Good Pharmacoepidemiology Practice (GPP), and applicable laws and regulations relating to the conduct of the study.

7.7 Data Analysis

A descriptive analysis of the distribution of values abstracted for each variable will be provided. For the continuous variables we are interested, the values of mean/median, standard deviation (SD), min/max, interquartile range (IQR, including the first quartile [Q1] and third quartile [Q3]) will be calculated; the frequency and percentages will be calculated for these categorical variables. Statistical comparisons will be conducted using chi-square test for categorical variables and Student’s t-test, Mann-Whitney U test, Kruskal-Wallis H test for continuous variables as appropriate. All analyses will be carried out using all available data. A participant with missing data on one variable will be used only in calculations that do not involve that variable.

All analyses will use SAS (SAS Institute Inc., Cary, North Carolina). Detailed statistical analysis plan (SAP) and corresponding mock-up tables/figures/listings will be described separately prior to the commencement of any analyses. Key points are listed below.

7.7.1 Primary Objective

7.7.1.1 Virologic suppression (VS) at Week 48±8 Following PIFELTRO™ or DELSTRIGO™ Administration

Number and proportion of patients with VS at week 48±8 will be calculated with a 95% CI in ART naïve and experienced HIV-1 infected adult Chinese patients with up to 48±8 weeks' treatment. The denominator denotes the number of patients who have data available to confirm the achievement of VS after 48±8 weeks' treatment of PIFELTRO™ or DELSTRIGO™, including:

- Patients who achieved VS at week 48±8;
- Patients who have viral load testing result without achieving VS at week 48±8;
- Patients who are confirmed as virologic failure before week 40.

HIV virologic information denotes plasma HIV-1 RNA quantitive/qualitative results. If the qualitative assay has a lowest limit of the detection of 200/500 HIV-1 RNA copies/ml of plasma, it will be excluded from the primary analysis. Any patient who has only one available HIV virologic information at week 48±8 and laboratory test results closest to 48-week time point (±8 weeks) will be used for the primary analyses. The patients with evidence of discontinuation (except virologic failure before week 40) during the observation period should be excluded for the primary analyses.

A subgroup analysis of an adherence cutoff of at least 80% will be used if data are available.

Results will also be stratified by patient sub-groups based on exposure to ART at the time of PIFELTRO™ or DELSTRIGO™ initiation, if applicable:

- ART naïve patients vs. ART experienced patients with or without virologic suppression
- ART naïve patients and ART experienced patients without virologic suppression vs. ART experienced patients with virologic suppression

7.7.2 Secondary Objective(s)

7.7.2.1 Baseline Demographic and Clinical Characteristics

The variables (Section 7.3.2.2 [Secondary outcomes]) will be described among patients in the study population overall, and separately by patients included and excluded from the effectiveness analyses. The variables will also be described among ART naïve and experienced HIV-1 infected adult Chinese patients, separately if applicable. Baseline demographic, baseline clinical characteristics (including comorbidities and VL) among ART naïve and experienced HIV-1 infected adult Chinese patients will be compared.

7.7.2.2 Treatment Patterns

The variables (Section 7.3.2.2 [Secondary outcomes]) will be described among patients in the study population overall, and separately by patients included and excluded from the effectiveness analyses.

For doravirine-included HAART discontinuation characteristics, frequency, proportion of patients with discontinuation, and time taken from the initiation to discontinuation will be reported. The reason for discontinuation will be classified and reported.

Additionally, descriptive analyses of adherence including medication variables will be reported.

7.8 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GPP, and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

7.9 Limitations of the Research Methods

The study has several important limitations inherent with the retrospective observational study design.

As this is an estimation not a comparator effectiveness study, it is not designed to a specifically compare PIFELTRO™ or DELSTRIGO™ treatment with other cART regimens The primary endpoint is assessed by laboratory values, so the design of the study is less likely to impact the measurement of virologic response. However, it is hard to make direct comparisons to clinical trial results. With this design the VS may be over- or under-estimated, due to factors such as adherence, persistence and possible unknown resistance to NNRTIs and other drugs included in ART using the retrospective multicenter observational study.

Second, all the clinical data is collected at point-of-care and is subject to the record-keeping practices of each healthcare provider and the standards of each clinic or organization. It is collected for the medical management of patients and is not directly intended for research purpose.

Third, due to NRDL update in the early 2022, PIFELTRO™ or DELSTRIGO™ treatment termination occurred, and this may impact on the patient number received PIFELTRO™ or DELSTRIGO™ treatment [redacted] The study may be not sufficiently powered, especially for naïve treatment subgroup.

Fourth, the selected hospitals or patients will not be randomly selected and may not be a representative sample of the whole PIFELTRO™ or DELSTRIGO™ administrated patients. At last, discontinuation of doravirine-included HAART may not be documented for most patients and the measures for observational studies is different from clinical trials, hindering our ability to directly compare the efficacy in real-world study with clinical trials.

Currently, medication is typically prescribed every 1-3 months for PIFELTRO™ or DELSTRIGO™ treatment in hospitals. On the one hand, patients go to the pharmacies outside the hospitals for refill in most site hospitals and the prescription information may not be reserved in some hospitals, each patient's data of prescribed medication for the entire period may not be accessed in the hospitals in this case. On the other hand, unlike the study medication diary in clinical trials, adherence through the prescription monitoring will result in inaccurate measurement of adherence. For example, patients may forget refill, drop the medicine or forget to take after refill, which will be regarded as adherence through the prescription monitoring. Thus, data from prescription monitoring will not be used for the effectiveness endpoint calculation and it may impact effectiveness estimation in real world.

7.10 Other Aspects

Not applicable

8 PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study, the study protocol and informed consent will be submitted for review and approval by an IRB/ERC prior to study execution. The privacy of all participants will be well protected, personal identification data will be de-identified at the time of analysis, including but not limited to name and ID and etc.

All demographic and diagnosis information for each eligible patients, as well as laboratory information are generated during the routine clinical practice and before the conduct of the retrospective chart review process. The information will be tracked, collected, stored and used by selected hospitals or the study staff of the retrospective study and will not be provided to entities outside the study.

8.1 Informed Consent

Given that the study is a retrospective medical chart review, the participating practitioner will submit the study to the IRB/ERC to let IRB/ERC determine whether the study qualifies to waive for informed consent.

In the situation where informed consent could not be waived, consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

9.1 Adverse Event and Product Quality Complaint Reporting

9.1.1 Investigator Responsibility

Although adverse events (AEs) and product quality complaints (PQCs) are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs

will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE* or PQC to PIFELTRO™ or DELSTRIGO™ or any other Sponsor product is identified, the AE/PQC must be reported according to Table 2. If any health outcomes are described in section 7.3.2, they must be assessed for AE reportability according to Table 2 (refer to section 9.1 for more information).

* For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 9.2 for definitions):

- Serious adverse reactions (SARs), including death
- Non-serious adverse reactions (NSARs)
- Special situations

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 2.

Table 2 AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	INVESTIGATOR TIMEFRAMES Investigator to Sponsor [1], [2]
SAR Serious Special Situation, regardless of causality	24 hours from receipt
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt
PQC with or without an AE (SAR/NSAR/Special situation)	24 hours from receipt
Follow-up to any AE/PQC-submit using above timeframes	
BD-Business Day; CD-Calendar Day	
Non-Sponsor Product: If the investigator elects to submit AEs/PQCs for **non-Sponsor products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.	
[1] Investigator to Sponsor: AEs and PQCs for Sponsor study product and *other* Sponsor products are submitted to the Sponsor for reporting to worldwide regulatory agencies as appropriate. **[2]** Study Lead ensures AEs for Sponsor study product are entered into study database (or equivalent repository) for tabulation in study report	
Submitting AEs and PQCs to China PV: All AEs and PQCs must be submitted to [redacted] in Chinese/English using the AE/PQC reporting form.	

9.1.2 Study Report

The final study report, and any planned interim analysis, will include a summary of all reported AEs and special situations collected for PIFELTRO™ or DELSTRIGO™ and will be provided to regulatory agencies by the Sponsor as required.

9.1.3 Periodic Safety Update Reports

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

9.2 DEFINITIONS

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered Sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

9.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

9.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 6.2.3.

9.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

9.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

9.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

9.2.8 Sponsor's Product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form for each reported event in relationship to a Sponsor's product.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed

should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

9.3 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs and PQCs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs and PQCs will be reconciled on a periodic basis.

9.4 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally. The results of this research study will be externally disseminated through the EU PAS Register. A manuscript may be submitted to a peer-reviewed, scientific journal or an abstract/presentation at a scientific conference or symposium.

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12 ANNEXES

Annex 1 List of Stand-Alone Documents

None.

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Annex 2 ENCePP Checklist for Study Protocols (Revision 4)

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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REVOPS ID NO: NIS101573 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08052.003	CORE DRC APPROVAL DATE: 28-JUL-2022

Study title: Post-marketing study to assess the effectiveness of Doravirine-included in highly active antiretroviral therapy (HAART) in HIV-1 infected adult Chinese patients

EU PAS Register® number:
Study reference number (if applicable): MK1439-088

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☒	☐	2
1.1.4 Interim report(s)	☐	☒	☐	2
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5.1
2.1.2 The objective(s) of the study?	☒	☐	☐	6.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

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Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	7.2.3
	4.2.2 Age and sex	☒	☐	☐	7.2.1
	4.2.3 Country of origin	☒	☐	☐	7.2.1
	4.2.4 Disease/indication	☒	☐	☐	7.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	7.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2.1, 7.4.1

Comments:

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Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	7.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	7.3.3

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

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Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	7.7

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
	9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

9.3 and 9.4 will be described in DMP.

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Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3	Are descriptive analyses included?	☒	☐	☐	7.7
10.4	Are stratified analyses included?	☒	☐	☐	7.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8
11.2	Are methods of quality assurance described?	☒	☐	☐	7.8
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	7.9
	12.1.2 Information bias?	☒	☐	☐	7.9
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.9

Comments:

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Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.1
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

It is an original version.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	5.1
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

No plan for publication.

Name of the main author of the protocol: PPD

Date: 28/Apr/2022

Signature: _____

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Annex 3 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence if applicable such information will be divulged to Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing

this protocol, the investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

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According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

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Annex 4 Qualified Person for PharmacoVigilance (QPPV)

Dr Guy Demol
PPD

MERCK SHARP & DOHME
Merck Sharp & Dohme (Europe) Inc.
Clos du Lynx, 5
1200 Woluwe-Saint-Lambert
Bruxelles, Belgique

PPD
PPD
Emergency/Out of Hours: GSM numbers above or via PPD

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN:
Product: PIFELTRO™(MK-1439) and DELSTRIGO™(MK-1439A)
Protocol No.: MK1439-088
Epidemiology No.: EP08052.003
Protocol Date: July 28th, 2022
MAH: Merck Sharp & Dohme LLC

In line with the Guideline on Good PharmacoVigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

PPD

Dr Guy Demol

PPD

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13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	PPD
TITLE	Associate Principal Scientist, Biostatistical and Research Decision Sciences (BARDS) Epidemiology MSD R&D (China) Co., Ltd.
SIGNATURE	
DATE SIGNED	

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13.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	PPD
TITLE	Professor, MD Department of Infection, Beijing Youan Hospital
SIGNATURE	
DATE SIGNED	

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13.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	PPD
TITLE	General Manager PPD
SIGNATURE	
DATE SIGNED	