TITLE: **Re**al World Utilisa**t**ion of **R**altegravir **O**nce Daily 1200mg

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Short Title:	RETRO study
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Summary of Changes

Summary of Changes for Amendment 1

Protocol Section	***Change***
Protocol summary; section 2.2; section 3.1	Safety timeline updated in the table and protocol body
Protocol summary; section 2.2; section 3.1; Section 4.3; section 8.1.2; section 8.2; section 8.2.1	Section titles updated for baseline and 6 months
Protocol summary; Section 3.1; Section 8.2; section 8.2.1	Extended timeline to December date
Section 6.2.5	Last bullet point to the Special Situations section* added
Section 7	Section 7 added
	Final CRF was submitted in this amendment for DRC Review

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List of Abbreviations

Drug Class Name	
AI	attachment inhibitor
INSTI	integrase strand transfer inhibitor
FI	fusion inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	nonnucleoside reverse transcriptase inhibitor
PI	protease inhibitor
General Terminology	
ADE	AIDS defining event
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral Therapy
BAA	business associates agreement
BID	twice daily
BHIVA	British HIV Association
CDC	Centers for Disease Control & Prevention
ELISA	enzyme-linked immunosorbent assay
EMA	European Medical Association
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP HBV	Good Pharmacoepidemiological Practice hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICD-9	International Classification of Diseases v9
IEC	Independent Ethics Committee
ISERP	Independent Safety Epidemiology Review Panel
IQR	Inter-Quartile Range
µL	Microlitre
mL	Millilitre
MTR	multiple tablet regimen
NSAR	Non-serious Adverse Reaction
OPERA	Observational Pharmaco-Epidemiology Research & Analysis
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
QA	quality assurance
QD / OD	once daily
RNA	ribonucleic acid
SAR	Serious Adverse Reaction
SD	Standard Deviation

STR	single tablet regimen
VL	viral load (HIV-1 RNA)

PROTOCOL SUMMARY

Full Title	Real World Utilisation of Raltegravir Once Daily 1200mg
Short title	RETRO study
Vendor/Collaborator	Adelphi Real World Ltd
Rationale	This study will provide data on patient characteristics and treatment patterns of HIV positive patients initiating raltegravir 1200mg once daily (RAL OD) (2 x 600mg). There is a lack of published real world data on the use of once daily raltegravir, and these data will show how RAL OD is used in the real world setting in the UK.
Primary Objective	To describe and understand the real world utilisation of RAL OD.
Primary Outcome measures	Description of patient demographics (age, gender, and ethnicity), baseline clinical and treatment characteristics (co-morbidities, co-medications, AIDS defining illnesses within the last 6 months/ever) in ART naïve and experienced HIV-1 infected adult subjects. Description of Antiretroviral therapy (ART) treatment combination initiated with RAL OD. If treatment experienced, description of prior ART regimen. Description of clinical and treatment characteristics (co-morbidities, co-medications) of subjects who remain on RAL OD at the 6 month time point. Description of any change in clinical and treatment characteristics from baseline to 6 months in subjects who remain on treatment
Secondary Data Collection Objective	Laboratory parameters at baseline and 6 months (HIV viral load, CD4 cell count), RAL OD discontinuations at 6 months
Study Design	Non-interventional, observational, multi-centre, retrospective chart review study
Study Population	HIV-1 infected adults initiating RAL OD as part of their ART at treatment centres within the UK from September 2017
Study Duration	The study duration is expected to be 6-12 months. Patient data will be collected on all patients starting RAL OD from September 2017 who return for their 6 month (-1/+3 months window) follow up appointment. Eligible patients

	must have completed their 6 month follow up before 31st December 2018
Exposure and Outcome	Exposure: RAL OD based ART Outcomes: descriptive utilisation and treatment patterns. Clinical measures (HIV viral load and CD4 cell counts) will be captured as secondary endpoints.
Statistical Methods	The profile of HIV-1 positive subjects initiating treatment with RAL OD will be analysed descriptively using summary statistics.
Sample Size and Power Calculations	Sample size of 300 across 2 centres. This is large enough to provide precise estimates overall and allow sub-group assessments. This will be a descriptive analysis - power calculations are therefore not applicable.
Limitations	Retrospective Database Analysis carries the potential for missing data. Non-randomised: Sampling limited to sequential systematic sampling due to treatment being newly available

1 Background and Rationale

1.1 Background

Highly active antiretroviral therapy (ART) has changed human immunodeficiency virus (HIV) infection from a fatal illness to a manageable chronic disease. Current British HIV Association (BHIVA) treatment guidelines for HIV infection recommend therapy naïve people living with HIV (PLWH) start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase strand transfer inhibitors (INSTI) (1). The INSTI class is the most recent class of drugs to be developed for HIV therapy. This group of medications appears to cause a more rapid decline in viral load when compared to PI or efavirenz (EFV) containing regimens. (2)

Raltegravir, 400 mg tablets twice daily (RAL BID), was the first agent of INSTI class approved for clinical use by the FDA in 2007(3). Multiple trials demonstrated RAL BID to be a very effective agent in both treatment-naïve and -experienced patients when used with either tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (4, 5) or abacavir (ABC)/lamivudine (3TC) (11, 12). RAL has demonstrated rapid HIV viral suppression and is considered to be a well-tolerated antiretroviral medication with few drug interactions, no food requirement, and a well-documented adverse effect profile in both treatment-naïve and -experienced, HIV-infected patients (2, 6). Due to lack of significant drug-drug interactions, RAL is a preferred option for patients on multiple medications (7).

RAL BID has the longest post-marketing experience of the INSTI class; both clinical trials and clinical experience have demonstrated durable virologic suppression in treatment-naïve and treatment-experienced patients, including patients with extensive antiretroviral experience and documented antiretroviral resistance.(7) A new 1200 mg, once-daily formulation of RAL (RAL OD), administered orally as two 600 mg tablets, was found to have non-inferior efficacy compared to RAL BID in a randomised clinical trial of treatment naïve HIV-1 infected patients (ONCEMRK).(8) RAL OD gained Marketing Authorization in July 2017 and was first available for prescription in September 2017. Once-daily regimens are often preferred by both patients and clinicians in order to facilitate adherence and improve patient quality of life. The RAL OD formulation administers a higher daily dose of raltegravir, as compared to RAL BID, in order to sustain sufficient trough concentrations (8).

1.2 Rationale

The ONCEMRK trial (8) evaluated RAL OD in treatment naïve HIV-1 infected patients. The extensive clinical experience with RAL BID will likely translate to the RAL OD formulation and influence the use of this new formulation. As RAL OD becomes more widely available for prescription, understanding the patient population in which it is preferentially prescribed (i.e. the patients' demographic and clinical profiles) as well as its overall effectiveness in clinical practice, may facilitate further insight as to its clinical impact in both ART naïve and experienced patients, including those switched from RAL BID, in the real world setting

2 Objectives and Hypotheses

2.1 Primary Objectives & Hypothesis

This study is purely descriptive, and as such no formal hypothesis will be tested.
It will explore how and to whom RAL OD is being prescribed in the UK outside of the clinical trial setting. Specific primary objectives are as follows:

- To describe demographic (age, gender, ethnicity), baseline clinical and treatment characteristics (co-morbidities, co-medications) in ART naïve and experienced HIV-1 infected adult subjects who have been initiated on RAL OD.

- To describe Antiretroviral Therapy (ART) treatment combination initiated with RAL OD.

- To describe prior ART regimen in treatment experienced subjects.

2.2 Secondary Objectives

The secondary study objectives are as follows:

- To describe clinical and treatment characteristics at 6 month (co-morbidities, co-medications) in subjects who have been initiated as above, and have data available at 6 month (-1/+3 months) follow up appointment, specifically:

  1. To describe:

     • Proportion of subjects still taking RAL OD
     • Proportion of patients with virologic suppression (<50 copies/ml) in ART naïve patients
     • Proportion of patients who maintain virologic suppression (<50 copies/mL) at follow up visit in ART experienced patients
     • Viral load in ART naïve patients.
     • Viral load in ART experienced patients
     • Percent and absolute change in CD4 cell count from RAL OD initiation
     • Proportion of patients with RAL OD discontinuation

  2. To describe characteristics of subsequent ARV regimens among patients who are switched from RAL OD based regimens to other ARV regimens.

  3. To describe change in clinical and treatment characteristics of patients who remain on RAL OD for the study time period.

3 METHODOLOGY

3.1 Summary of Study Design

This is a non-interventional, retrospective observational chart review study at 2 UK treatment centres that will utilize electronic data capture (EDC) to address study objectives.

The study will capture data from 300 HIV-1 positive adult subjects receiving RAL OD as part of their ART at UK NHS treatment centres. NHS records generally capture all of the usual care of an HIV positive patient including their physical exams, diagnoses, laboratory findings, medication prescriptions, co-morbidities, social history and demographic data.

All eligible HIV-1 infected adult patients (≥ 18 years) who initiated RAL OD based ART from September 2017 will be included in this study on a sequential sampling basis. Data from eligible patients' medical charts will be extracted for the time of initiation and at 6 months (window of -1/+3 months) post-initiation follow up appointment.

The index ARV regimen is defined as the first RAL 1200mg OD (2 x 600mg) containing ARV regimen a patient receives and the baseline will be defined as the RAL 1200mg OD

initiation prescription date. Treatment with RAL OD must have been initiated during or after September 2017 and before April 1st 2018 for the primary baseline data collection. Subjects should have at least one 6 month (-1/+3 months) follow up appointment before December 31st 2018 to ensure 6 month secondary outcomes data are available for analysis. Chart review will only be carried out once a patient has completed the 6 month visit to ensure all data are captured retrospectively.
This time period was selected based on expectations of RAL OD utilization over time in the post-launch period and standard UK practice of 6-monthly clinic appointments.

The final analysis will be conducted following database lock after the last study participant has reached the 6 (-1/+3) months treatment milestone, by December 31st[h] 2018, and all data queries have been resolved.

3.2 Study Population

The study will be conducted in 2 NHS hospital HIV departments in the UK. To ensure the data are representative of the UK, centres will be chosen to represent London and non-London in proportion with the treated patient population. As approximately 50% of UK HIV patients are treated in London, one of the potential sites will be selected from the largest treatment centres in London. The additional site will be a non-London treatment centre, and will be selected primarily based on the number of eligible patients treated.
Patients who were initiated on RAL OD at least 6 months ago will be identified by the clinician, Principal Investigator or a member of the clinical team, from review of hospital records and databases as appropriate at each centre. From a list of eligible patients with the required data, the earliest recent record will be recorded as the first participant and then all further eligible participants up to 150 per centre will be selected sequentially to minimize bias.

It is intended that approximately 150 patients will be included from each participating centre to represent a proportionate spread. Oversampling may be performed in the larger centre in order to maintain an overall sample size of 300.

3.3 Inclusion Criteria

HIV-1 infected patients initiating RAL OD based ART during or after September 2017 and before April 30th 2018 will be included in the study sample if they meet the following inclusion criteria:

1) A diagnosis of HIV-1 infection

2) At least 18 years of age at the index date

3.4 Exclusion Criteria

1) Patients co-infected with HIV-2. (A diagnosis of HIV-2, a positive HIV-1/HIV-2 Multispot, a positive HIV-2-specific ELISA and/or a positive HIV-2 Western Blot will all be considered evidence of HIV-2 coinfection.)

2) Patients who initiated RAL OD or other ART as part of a clinical trial.

4 Variables and Epidemiological Measurements

4.1 Exposure

Subjects treated with RAL OD will be identified by the administering clinicians within the treatment centres. Unless they discontinue treatment during the study period, subjects will have been taking RAL OD for at least 6 months.

4.2 Outcomes

The main outcome of this study will be a description of the demographic variables, clinical, and treatment characteristics of people who are initiated on RAL OD in real-life clinical practice in the UK. Virologic and immunologic variables will also be recorded.

4.3 Covariates

Demographic variables at baseline

- Gender: male including trans male/female including trans female. Is this the gender assigned at birth yes/no
- Post-menopausal woman yes/no
- MSM yes/no
- Age
- Ethnicity: White, Black African, Black Caribbean, Black other, Asian, Other/mixed

Virologic variables at baseline and 6 months

- HIV viral load in ART naïve patients
    - Baseline
        - Continuous (copies/mL): Median (IQR)
        - Categorical:
            - <1,000 copies/mL
            - ≥1,000 copies/mL to < 10,000 copies/mL
            - <10,000 copies/mL
            - ≥10,000 to <100,000 copies/mL
            - ≥100,000 copies/mL
    - 6 month
        - Continuous (copies/mL): Median (IQR)
        - Categorical:
            - <50 copies/mL

- 50 to <200 copies/mL
- 200 to <1,000 copies/mL
- ≥1,000 copies/mL to < 10,000 copies/mL
- <10,000 copies/mL
- ≥10,000 to <100,000 copies/mL
- ≥100,000 copies/mL

- HIV viral load in ART experienced patients at baseline and 6 months
  - Continuous (copies/mL): Median (IQR)
  - Categorical:
    - <50 copies/mL
    - 50 to <200 copies/mL
    - 200 to <1,000 copies/mL
    - ≥1,000 copies/mL

Immunologic variables at baseline and 6 months

- CD4 cell count and CD4 % in ART naïve and experienced patients
  - Continuous (cells/mL)
  - Categorical:
    - > 500 cells/mL
    - >350 to ≤500 cells/mL
      >200 to ≤350 cells/mL
      <200 cells/mL

HIV-specific clinical variables at baseline

- RAL OD initiation date
- ART Naïve (yes/no)
- ART experienced (yes/no)
- Prior ART regime if treatment experienced as below (tick box):

  NRTI:
  - ABC + 3TC
  - TDF + FTC
  - TAF + FTC

  Third agent:
  - dolutegravir
  - atazanavir boosted with ritonavir
  - elvitegravir boosted with cobicistat
  - darunavir boosted with ritonavir
  - raltegravir (400mg bd; other please specify)
  - rilpivirine

  Other ART:
  - please specify

- Pill burden (number of ART pills)
- AIDS defining illnesses[9] ever (yes/no)
- AIDS defining illnesses[9] within the past 6 months (yes/no)

Other Clinical Variables at baseline

- Smoking Status (current, previous, never, unknown)
- Recreational Substance Use (excluding alcohol and tobacco)
- ChemSex (yes/no/unknown)

Comorbidities (Presence of the condition).

- Acid Reflux
- Anaemia
- Anxiety Disorders
- Cancer
- Cardiovascular (any) except hypertension
- Moderate/Severe Chronic kidney disease
- Depression
- Diabetes mellitus
- Hepatitis B
- Hepatitis C
- Hepatitis, Other e.g. alcohol/drug related, autoimmune
- Hepatic Impairment: Child-Pugh or Model for end stage liver disease (MELD)[10]
- Hyperlipidaemia
- Hypertension
- Osteopenia
- Osteoporosis
- Schizophrenia/Bipolar or Manic Disorder
- Vitamin D deficiency
- Other co-morbidity

Concomitant non-ARV medications

- lipid-lowering agents
- antihypertensive agents
- anti-inflammatory agents (NSAIDs)
- psychotropic agent (hypnotic, antidepressant and antipsychotic)
- anti-infective agents
- acid suppressants (proton pump inhibitor and H2 antagonist)
- anti-diabetics/insulin
- bone-protecting agents
- methadone

- vitamins, herbal treatment (please specify)
- other prescribed medication (please specify)
- other non-prescribed medication (please specify)
-

5 STUDY PROCEDURES

5.1 General Informed Consent

This is a retrospective chart review of RAL OD use among patients at UK centres. As such individual informed consent from subjects will depend on site requirements. Some sites might have a general consent form signed by the patients to stipulate that their data can be used for research. Some other sites might not need informed consent for retrospective chart reviews. Site requirement for informed consent will be documented in the study master filing.

5.2 Data collection

A separate data collection tool will be provided for each centre to enter its patient data. The tool will be structured to prevent the collection, use, or transmission of individual identifiable data. Selected study centres will conduct their own chart review for this purpose – MSD personnel will not come into contact with source data for any patient.

6 Safety Reporting and Related Procedures

This is a non-interventional chart review 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 additional procedures required as part of this protocol.

6.1 Adverse Event Reporting

6.1.1 INVESTIGATOR RESPONSIBILITY:

Although adverse events are not actively solicited in this study, there are certain circumstances in which individual adverse events 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 a serious adverse reaction (SAR), including death, or a non-serious adverse reaction (NSAR) to RAL or any other MSD product is identified, the event must be reported according to Table 1.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAR/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

Table 1: AE Reporting Timeframes and Process for Investigators and Vendors

EVENT TYPE	INVESTIGATOR TIMEFRAMES	VENDOR TIMEFRAMES
	Investigator to Vendor [1], [2]	**Vendor to MSD [4]**
SAR Pre-specified HOI that meets criteria of SAR Serious Special Situation, regardless of causality	24 hours from receipt	1 BD/3 CD (whichever is shorter) from time of receipt from investigator
NSAR Pre-specified HOI that meets criteria of NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt	1 BD/3 CD (whichever is shorter) from time of receipt from investigator
Spontaneously reported adverse events for MSD products-submit using above timeframes		
If the investigator elects to submit AEs for **non-MSD 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.		
Follow-up to any event-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
[1] AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilized. **[2] Investigator to Vendor**: Applies to events for **MSD study product**, and ***other*** **MSD products** when a VENDOR is managing AE reporting from investigator to MSD. Events for **MSD study product** are entered in study database for tabulation in study report. Events for ***other*** **MSD products** are *not entered in study database* but must be forwarded to MSD via Vendor for regulatory reporting. **[3] Investigator to MSD:** Applies to studies that do not have a vendor managing AEs. **[4] Vendor to MSD:** Applies to events for **MSD study product** and ***other*** **MSD products** if the vendor is managing AE reporting between investigator and MSD. Not applicable for studies not using a vendor for AE reporting.		

Submitting AE reports to Vendor: The Investigator must submit all AEs to the vendor as per the timelines specified in table 1 by fax at 01625 557294.
Submitting AE reports to MSD Global Safety: The vendor must submit all AEs as per the timelines mentioned in table 1 by fax to MSD UK Pharmacovigilance Department at 0032 2402 5990 or via password protected secure email to pv.uk@merck.com, in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate.

6.1.2 STUDY REPORT:

The final study report, and any planned interim analysis, will include aggregate listings of all events collected for RAL and will be provided to regulatory agencies by the sponsor as required.

6.1.3 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.

6.2 DEFINITIONS

6.2.1 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.

6.2.2 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.

6.2.3 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.

6.2.4 Non-serious Adverse Reaction (NSAR)

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

6.2.5 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

6.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such..

6.2.7 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.

6.2.8 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.

6.5 Sponsor Responsibility for Reporting Adverse Events

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

7 Product Quality Complaint Reporting

Although product quality complaints are not actively solicited in this study, there are certain circumstances in which individual Product Quality Complaints (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 a PQC to any MSD product is identified, the PQC must be reported by the study investigator or qualified designee using the Product Quality Complaint (PQC) Reporting Form following the instructions in Table 2. The PQC Reporting Form must be fully completed in English. Once the PQC Reporting Form is submitted, the investigator or designee may be contacted for further information.

If both an AE and a PQC occur, the AE should be reported according to the AE reporting requirements in the protocol and the PQC should be reported per Table 2.

EVENT TYPE	**INVESTIGATOR TIMEFRAME**
	Investigator to MSD
PQC	24 hours from receipt
PQC reports must be submitted via e-mail by the investigator to the local designated point of contact (DPOC) using a PQC form.	
Submitting PQC reports to MSD: All PQCs must be submitted to the local DPOC in English using a PQC form (attached) **via secure (password protected) email to dpoc.uk@merck.com**	

7.1 DEFINITIONS

7.1.1 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.

7.1.2 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.

8 Statistical Analysis Plan

Detailed description of the statistical analyses, any deviation from the protocol, and assumptions employed will be presented in a detailed Statistical Analysis Plan (SAP) that will be prepared prior to database closure and initiation of any statistical analyses.

All analyses will be conducted on the per protocol population unless otherwise stated in the sections below. Missing data will not be imputed, and all analyses will be based on observed data only.

8.1 Statistical Methods

8.1.1 Primary Objective(s):

a) Demographics and description of RAL OD patients
The demographic characteristics of all subjects starting RAL OD (Gender; menopausal status, Age, Ethnicity) will be presented as summary statistics (mean, median, standard deviation, IQR, maximum, minimum and for continuous measurements and numbers and proportions for categorical measurements)
b) Clinical and treatment characteristics (co-morbidities, co-medications, baseline ART)
Clinical and treatment characteristics of all subjects initiating treatment with RAL OD will be analysed descriptively using summary statistics. These will include the mean, median, standard deviation, and 95% confidence interval of the mean for continuous variables and frequency distributions for categorical variables.

8.1.2 Secondary objectives

a) Clinical and treatment characteristics (co-morbidities, co-medications, ART, discontinuations)

Clinical and treatment characteristics and changes from baseline in all subjects who have data available at the follow up appointment will be analysed descriptively using summary statistics. These will include the mean, median, standard deviation, and 95% confidence interval of the mean for continuous variables and frequency distributions for categorical variables.

b) Virologic and immunologic outcomes

Virologic and immunologic outcomes will be analysed descriptively at baseline and follow up appointment. Test results closest to the 6 month time point will be used for these analyses.
Frequency and proportion of patients with virologic suppression (Section 3.1) at baseline and 6 months will be described.

Among the virologically suppressed patients at baseline, frequency and proportion of patients with sustained virologic suppression, and viral load measures (Section 3.1) at 6

months will be described. Data will be presented as the mean, median, interval of the mean for continuous variables and frequency distributions for categorical variables. A mean change from RAL OD initiation in CD4 cell count will be described at the 6 month time point.

Per Protocol Analysis: Primary Objective = All subjects who initiated RAL OD treatment.
Secondary Objective: Numerator = patients who remained on RAL OD treatment for the 6 month study period; Denominator = all patients who initiated RAL OD therapy.

8.2 Bias

It is intended that data will be collected on consecutive patients in who at least 6 months follow-up was possible (i.e. started RAL OD during or after September 2017). Eligible patients must have completed their 6 month follow up before 31st December 2018. This will include any patients who may have moved treatment centres since initiation.
Participating centres will be selected to be representative of the UK population, one site from within London (where approximately 50% of HIV patients in the UK are currently treated) and one from outside London will be used.
The study is a retrospective chart review study that will be using data extracted from databases; any missing data will be queried with the sites and if not available, will be recorded as such.
Any observational study has the possibility of residual confounding due to unknown risk factors [13]. However this study is designed to collect information on recent prescribing practice and is based on clinical experience and knowledge of the HIV physician.

8.2.1 Methods to Minimize Bias

By including 2 treatment centres we hope to reduce single centre bias. Furthermore, to minimise bias and to ensure a sample population which is representative of UK, site selection will be based on treatment hubs within areas of high prevalence.
As approximately 50% of UK HIV patients are treated in London one of these treatment centres will be randomly selected from the 6 largest treatment centres in London. The other treatment centre will be a non-London centre.
Patients who from September 2017 were initiated on RAL OD for at least 6 months and who completed their 6 month follow up before 31st December 2018, up to 150 patients per site initially, will be selected sequentially to minimise bias. Should the larger site continue to recruit additional patients in order to meet the target of 300, the same methods will be used.

8.2.3 Limitations

The results of the study must be interpreted in consideration of the known limitations of chart review studies. Specifically, the use of data extracted from medical charts carries a possibility of information bias related to the validity of the data reported by the service providers, including missing, inconsistent or erroneous information, and the likelihood of human error during transcription.
Furthermore, given that the current study is a retrospective study that will be using data extracted from medical charts, it will not be possible to retrieve any missing data. However, cross-validation will be performed and erroneous data will be clarified with the physicians or delegates.

8.3 Sample Size and Power Calculations

Sample size will depend on the uptake and capture of RAL OD data in the selected sites. The uptake of RAL OD in these sites is expected to be sufficient to assess the primary objective of characterising the initial utilisation of RAL OD in 300 subjects, provide precise estimates overall, and allow sub-group assessments.
As this is a descriptive study no power calculations will be carried out.

9 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 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, and such information will be divulged to the 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.

9.1.2 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. By signing the consent form, the subject agrees to this process. 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.

9.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and study site personnel, 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. 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. By signing this protocol, the investigator expressly consents to these uses and disclosures.

As this is a multicentre 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.

9.2 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/sub-investigator's responsibility to comply with any such request.

The investigator/sub-investigator(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/sub-investigator(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/sub-investigator(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.

9.3 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 (GPP) 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 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.

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, MSD, 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.

9.4 Compliance with Study Registration and Results Posting Requirements

The study will be posted on EnCEPP in accordance with MSD processes

9.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable laws, rules and regulations relating to the conduct of the study.

9.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that

his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

10 Publications

Study results will be disseminated as posters or oral presentations at BHIVA, submission mid Jan 2019, and EACS, submission Q2/3 2019. The results will also be published in an end of study report for the Sponsor and submitted as a paper to a peer-reviewed academic journal, and subsequently posted on EnCePP.

11 References

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11. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013; 381: 735–43.

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11 Appendices

APPENDIX A

Conditions included in the CDC 1993 Revised Classification System for HIV Infection and expanded Surveillance Case Definition for AIDS.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive *
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary * or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent *
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

*Added in the 1993 expansion of the AIDS surveillance case definition.

12 Attachment

13 SIGNATURES

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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 manuals and documents referenced from this protocol); deviations 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 serious adverse experiences as defined in Section 6 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, 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.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____