# NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

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|---|---|
| **Study Title** | A Prospective, Longitudinal, Observational Registry of Truvada for HIV-1 Pre-Exposure Prophylaxis (PrEP) of Adults and Adolescents in Europe |
| **Protocol ID** | GS-EU-276-4487 |
| **Protocol Version/Date:** | 1.0 21 March 2018<br>1.1 17 August 2018<br>1.2 28 March 2019<br>1.3 20 August 2019<br>1.4 20 January 2020 |
| **EU PAS Register No** | To be registered |
| **Active Substance** | Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/245 mg film-coated tablets |
| **Medicinal Product** | Truvada® |
| **Product Reference** | EU/1/04/305/001<br>EU/1/04/305/002 |
| **Procedure Number** | NA |
| **Joint PASS** | No |
| **Research Question and Objectives** | The objectives of this registry are to: (1) Describe how Truvada for PrEP is prescribed or self-initiated, including the dosing pattern (dose and schedule as daily/intermittent); (2) Characterize the demographics of adults and adolescents who were prescribed or are taking Truvada for PrEP and their HIV risk factors; (3) Characterize the nature and frequency of individual monitoring after initiating Truvada for PrEP, including any available information on adherence; (4) Document any cases of new HIV diagnoses and development of any resistance to Truvada, and selected safety data; and (5) Summarize the characteristics of healthcare professionals who prescribe Truvada for PrEP. |
| **Countries of Study** | Belgium, France, Norway, Portugal, and Sweden |
| **Gilead Study Director / Author / Contact Person** | Name: PPD<br>Telephone: PPD |
| **Marketing Authorization Holder** | PPD |
| **MAH Contact Person** | Name: PPD<br>Telephone: PPD |

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| **Gilead Qualified Person Responsible for Pharmacovigilance** | Name: | PPD |
| | Telephone: | PPD |

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# 2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| ADR | adverse drug reaction |
| CRO | contract research organization |
| DP | diphosphate |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| EU | European Union |
| F | female |
| FTC | emtricitabine |
| GPP | Good Pharmacoepidemiology Practices (guidelines for) |
| Gilead | Gilead Sciences/Gilead Sciences, Inc. |
| GVP | Good Pharmacovigilance Practices |
| HBV | hepatitis B Virus |
| HCP | Healthcare Professional |
| HCV | hepatitis C Virus |
| HIV-1 | Human Immunodeficiency Virus Type 1 |
| HMA | Heads of Medicines Agencies |
| ICH | International Council for Harmonisation (of Technical requirements for Pharmaceuticals for Human Use) |
| IEC | independent ethics committee |
| M | male |
| MSM | men who have sex with men |
| PAS | post-authorization study |
| PASS | post-authorization safety study |
| PrEP | pre-exposure prophylaxis |
| PEP | post-exposure prophylaxis |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PVE | Pharmacovigilance and Epidemiology. A department at Gilead Sciences that was renamed to Pharmacovigilance and Epidemiology (PVE), effective 01 December 2017. |
| SADR | serious adverse drug reaction |
| SAE | serious adverse event |
| SmPC | summary of product characteristics |
| TDF | tenofovir disoproxil fumarate |

# 3. RESPONSIBLE PARTIES

**Table 3-1. Responsible Parties**

| Responsibility | Name, Title, Qualifications, Affiliation, Address | Contact Information |
|---|---|---|
| Marketing Authorization Holder | Gilead Sciences Ireland UC<br>PPD | Email: PPD<br>Phone: PPD |
| Study Director | PPD<br>Executive Director, Epidemiology<br>PPD | Email: PPD<br>Phone: PPD |
| Clinical Operations | PPD<br>Clinical Program Manager<br>PPD | Email: PPD<br>Phone: PPD |
| Pharmacovigilance | Pharmacovigilance and Epidemiology (PVE)<br>PPD | Email: PPD<br>Phone: PPD<br>Fax: PPD |
| EU QPPV | PPD<br>Vice President, PVE<br>PPD | Email: PPD<br>Phone: PPD |

# 4. PROTOCOL SYNOPSIS/ABSTRACT

**Gilead Sciences, Inc.**
**333 Lakeside Drive**
**Foster City, CA 94404, USA**

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|---|---|
| **Title:** | A Prospective, Longitudinal, Observational Registry of Truvada for HIV-1 Pre-Exposure Prophylaxis (PrEP) of Adults and Adolescents in Europe |
| **Rationale and Background:** | A European Commission Decision was received on 18 August 2016 for a Type II Variation for Truvada® (emtricitabine/tenofovir disoproxil fumarate; FTC/TDF) to extend the indication to include PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. A subsequent European Commission Decision was adopted on 05 February 2018 for a Type II Variation to expand the indication for PrEP to adolescents weighing at least 35 kg, in accordance with the agreed pediatric investigation plan for Truvada.<br><br>The Truvada summary of product characteristics (SmPC) states that Truvada is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk.<br><br>This registry is designed to collect real-world data on use of Truvada for PrEP in adults and adolescents in Europe. |
| **Research Question and Objectives:** | The objectives of this voluntary participation registry are as follows:<br>1) To describe how Truvada for PrEP is prescribed or self-initiated, including the dosing pattern (dose and schedule as daily/intermittent)<br>2) To characterize the demographics of adults and adolescents who were prescribed or are taking Truvada for PrEP and their HIV risk factors<br>3) To characterize the nature and frequency of individual monitoring after initiating Truvada for PrEP, including any available information on adherence<br>4) To document any cases of new HIV diagnoses and development of any resistance to Truvada, and selected safety data<br>5) To summarize the characteristics of healthcare professionals who prescribe Truvada for PrEP |
| **Study Design:** | This will be a prospective, longitudinal, observational, and voluntary participation registry of the real-world usage of Truvada |

for PrEP to prevent HIV-1 infection in adults and adolescents in Europe. Due to the restricted availability of Truvada for PrEP in various European countries, this registry will initially be conducted in a limited number of European countries where Truvada for PrEP is being reimbursed. Initially, the target countries to be included in the registry will be Belgium, France, Norway, Portugal, and Sweden. Other countries may be included following reimbursement approval of Truvada for PrEP. Within each of the countries where drug utilization will be assessed, representative healthcare institutions (where biomedical interventions for HIV prevention are being prescribed) and institutions with individuals who have discontinued participation in clinical studies or demonstration projects with Truvada for PrEP will be assessed for feasibility to participate in this registry which will focus on all individuals receiving Truvada for PrEP. This registry will not provide Truvada.

Both male and female adults and adolescents will be recruited for enrollment in the registry. Individuals who started Truvada for PrEP prior to first presenting to the participating healthcare professional (HCP) or are prescribed Truvada for PrEP will be eligible for enrollment. Individuals receiving Truvada for PrEP will be followed and relevant demographic and ongoing use data will be collected in the registry. The individuals who agree to participate in the registry will receive treatment solely based on current clinical practice in the country in which they reside. The use of Truvada for PrEP should be within the conditions of its approved SmPC. However, Gilead will not influence decision making by the participating HCPs or restrict enrollment into the registry to those individuals who are not receiving drug in full compliance with the SmPC (where local regulations allow to do so) as the objective of the registry is to describe the patterns of use and monitoring in real life. Data on intermittent use of Truvada for PrEP will be collected in countries permitting such data collection. The frequency of clinic visits will be at the discretion of the prescriber.

Details on the product prescribed, the healthcare institution characteristics, and prescriber characteristics will also be collected.

Country-specific protocols may be developed to comply with local regulations on data collection. Gilead will work with a contract research organization to develop and launch the registry.

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| **Population:** | Both adults (≥ 18 years of age) and adolescents weighing at least 35 kg (eg, 12 to 17 years of age) receiving Truvada for PrEP will be included as the primary population for this registry. Furthermore, the registry will collect data on HCPs who prescribe Truvada for PrEP.<br><br>Inclusion criteria:<br><br>• HIV-1 negative adults and adolescents who are deemed to be at high risk for acquiring HIV-1<br><br>• HIV-1 negative adults and adolescents who provide consent / assent and, depending on local country regulations, parental or legal guardian permission to participate in the registry<br><br>• HIV-1 negative adults and adolescents who are receiving Truvada for HIV PrEP, either as a daily or intermittent regimen, and that are clinically monitored<br><br>Exclusion criteria:<br><br>• Individuals currently participating in a clinical study of HIV PrEP |

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| **Variables:** | Individual data elements will be collected as available after enrollment and while participating in the registry. Data will include: age, gender at enrollment, weight and height, HIV risk factors, concurrent sexually transmitted infections, hepatitis B virus serostatus, hepatitis C virus serostatus, prior PrEP or post-exposure prophylaxis use, estimated glomerular filtration rate, serum phosphate, use of recreational drugs during sex, and PrEP adherence assessment. Pregnancy status will be requested for females. PrEP prescription/usage details will include: dose schedule, initiation (ie, prescription or self-initiation) date and stop date or duration of PrEP usage, and the tablet and refill quantity. If seroconversion occurs, additional data include date of seroconversion, circumstances of HIV acquisition if available, and results of HIV-1 resistance testing if available. Selected safety data for collection in the registry will include all fatal events, serious adverse drug reactions (SADRs), treatment-related renal or bone adverse drug reactions, and pregnancy reports. Possible factors leading to new HIV infection, genotypic resistance testing, and reason for PrEP discontinuation will also be collected.<br><br>Details on the participating institutions will include location and type of institution. HCP data will include provider specialty and if they routinely treat individuals with HIV-1 infection. |
| **Data Sources:** | Prescriber information will be collected at enrollment. Available clinical and laboratory data will be collected by HCPs from medical records at treatment initiation and at follow-up time points (eg, initiation of PrEP, clinic visits, discontinuation of PrEP, and at time of HIV-1 seroconversion if applicable). |
| **Study Size:** | The purpose of the registry is to provide insight into the patterns of Truvada for PrEP usage and how clinicians are monitoring individuals on Truvada for PrEP. The registry is not designed or powered to compare rates of seroconversion or adherence with studies or demonstration projects.<br><br>Enrollment will be open to both adults and adolescents and individuals will be followed while Truvada for PrEP is continued. Target is to enroll and follow enough adults to provide at least 400 person-years of follow-up data and enough adolescents to provide at least 25 person-years of follow-up data. |
| **Data Analysis:** | Descriptive analyses will be used to summarize the available data. There are no statistical hypotheses to evaluate. Categorical variables will be reported by proportions and continuous variables will be reported by mean, standard deviation, minimum, median, and maximum. Prescriber characteristics will be summarized. |

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| | Demographics and clinical characteristics of individuals on Truvada for PrEP will be analyzed. The products prescribed and available prescription details including duration of PrEP, the frequency of monitoring, any relevant data on adherence monitoring, and reported safety events (fatal events, SADRs, renal or bone ADRs) will be summarized. Seroconversion cases and results of resistance testing will be summarized. Reported pregnancies will also be analyzed.<br><br>Rates of adherence and new HIV diagnoses (ie, seroconversion) will be calculated with 95% confidence intervals. Results will be presented overall and by subgroups including adults and adolescents, gender, and country. |
| **Milestones:** | Start of data collection: Target start date of data collection is end of Q4 2020 (after Pharmacovigilance Risk Assessment Committee [PRAC] approval of the protocol).<br><br>End of Data collection: Enrollment will be open for 3 years after the first individual enrolls. Data collection will continue for 6 months after the 3-year enrollment period, estimated to be completed by Q2 2024.<br><br>Interim report: Interim reports will be prepared annually after opening enrollment, estimated for Q4 in 2021 and 2022.<br><br>Final report: A final report will be submitted within 12 months of end of data collection, estimated for release before Q2 2025. |

This registry will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

# 5. AMENDMENTS AND UPDATES

**Table 5-1. Protocol Amendments and Updates**

| Amendment or Update Number | Date | Section of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| Version 1.1 | 17 August 2018 | Entire protocol | Update | Protocol revised based on comments from the PRAC. Due to the data gap regarding use of HIV PrEP in adolescents and young adults, the registry was revised to focus enrollment and data collection on adolescents and young adults |
| Version 1.2 | 28 March 2019 | Entire protocol | Update | Protocol revised based on discussions with the PRAC to develop a survey of healthcare professionals to capture data on PrEP usage across the EU |
| Version 1.3 | 20 August 2019 | Entire protocol | Update | Protocol revised based on discussions with the PRAC to develop a registry for both adults and adolescents taking PrEP |
| Version 1.4 | 20 January 2020 | Entire protocol | Update | Protocol revised based on comments provided from the PRAC including removal of reference to generic FTC/TDF |

PRAC Pharmacovigilance Risk Assessment Committee

## 5.1. Protocol Modifications

Protocol modifications may be made only by Gilead Sciences.

# 6. MILESTONES

**Table 6-1. Registry Milestones**

| Milestone | Planned Date |
|---|---|
| Start of data collection | The registry will be opened for recruitment in each of the selected countries after approval/notification by the relevant National Competent Authority and Ethics Committee as required.<br>Target start date of data collection is end of Q4 2020. |
| Enrollment period | 3 years<br>(Q4 2020 until Q4 2023) |
| End of data collection | 6 months after enrollment of the last individual<br>(Q2 2024) |
| Interim report 1 | 1 year after first enrollment<br>(Q4 2021) |
| Interim report 2 | 2 years after first enrollment<br>(Q4 2022) |
| Registration in the EU PAS register | Prior to Start of Enrolment<br>(Q4 2020) |
| Final report of study results | A final report will be submitted within 12 months of end of data collection<br>(Prior to Q2 2025) |

# 7. RATIONALE AND BACKGROUND

## 7.1. Rationale for the Current Study

A European Commission Decision was received on 18 August 2016 for a Type II Variation for Truvada® (emtricitabine/tenofovir disoproxil fumarate; FTC/TDF) to extend the indication for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. A subsequent European Commission Decision was adopted on 05 February 2018 for a Type II Variation to expand the indication for PrEP to adolescents weighing at least 35 kg, in accordance with the agreed pediatric investigation plan for Truvada.

The Truvada summary of product characteristics (SmPC) states that Truvada is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk.

The incidence of HIV infections in the European Union (EU) and European Economic Area for 2017 is estimated at 6.2 per 100,000 people {World Health Organization (WHO) 2018a}. The rates per country varied across countries, including 4.4 per 100,000 people in Sweden, 6.7 per 100,000 people in the United Kingdom, 7.9 per 100,000 people in Belgium, 8.2 per 100,000 people in France, and 14.2 per 100,000 people in Portugal. Males who have sex with males accounted for 38.2% of cases of new HIV infections.

The safety and efficacy of once daily oral Truvada in the prevention of HIV-1 acquisition among men who have sex with men (MSM) have been demonstrated in a large (n 2499), multinational, randomized, placebo-controlled, double-blind, Phase 3 study (also known as the PrEP Initiative [iPrEx] study [CO-US-104-0288]){Grant et al 2010}. The safety and efficacy of once daily oral Viread® (tenofovir disoproxil fumarate) or Truvada in the prevention of HIV-1 acquisition among East African heterosexual men and women in 4747 HIV-1 serodiscordant partnerships were demonstrated in a randomized, placebo-controlled, double-blind, Phase 3 study (also known as the Partners PrEP study){Baeten et al 2012}.

The WHO Implementation Tool for Pre-Exposure Prophylaxis (PrEP) of HIV Infection, Module 12 Adolescents and Young Adults (released July 2018) identifies adolescents and young adults as a high risk group for acquiring HIV and accounts for 37% of the new HIV infections {World Health Organization (WHO) 2018b}.

Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN113) in which 67 HIV-1 uninfected adolescent MSM received Truvada once daily for PrEP {Hosek et al 2017}. The mean age of subjects was 17 years (range 15 to 18 years); 46% were Hispanic, 52% black, and 37% white. No new adverse drug reactions (ADRs) were identified in Study ATN113.

In Study ATN113, no seroconversions occurred in any subject who had tenofovir diphosphate (TFV-DP) levels associated with protection against rectal HIV exposure. HIV seroconversion occurred in 3 subjects: 2 subjects with TFV-DP levels below the limit of quantitation and 1 subject with TFV-DP levels that correlate with < 2 doses per week on average (< 350 fmol/sample). No tenofovir- or emtricitabine-associated HIV-1 resistance mutations were detected in the 3 seroconverters. The incidence rate for new HIV infections (seroconversion) is 6.4% (6.4 per 100 person-years). Adherence in adolescents in Study ATN 113 was assessed by dried blood spot, which demonstrated that 55% of adolescents 15 to 17 years of age at Week 12 had dried blood spot TFV concentrations of > 700 fmol/punch, consistent with taking at least 4 Truvada tablets per week.

The Amsterdam PrEP demonstration project reported that in 269 adults (≥ 18 years) taking Truvada for PrEP on a daily basis and followed for up to 2 years, the incidence rate for new HIV infections (seroconversion) is 0.4% (0.4 per 100 person-years) {Hoornenborg et al 2019}.

Data on the use of Truvada for PrEP in adults have been generated from controlled clinical studies and more recently in observational studies and PrEP demonstration projects. Data on the use in adolescents and young adults are however limited. This registry is designed to collect real-world data on use of Truvada for PrEP in adults and adolescents in Europe.

7.2 Rationale for differences to Non-Interventional Study Design Requirements This registry will have a focused safety data collection approach, as specified below, to meet the key objectives of the registry without adding additional overhead data collection with limited scientific value for the purposes of the registry. Gilead has requested a waiver from standard collection of AEs for this noninterventional post-authorization safety study (PASS), which was agreed upon by PRAC

Per Good Pharmacovigilance Practices (GVP) Module VIII, noninterventional PASS should use the medicinal product in accordance with the terms of the marketing authorization. Truvada for PrEP is approved for daily administration. However, in order to meet the objectives of interest to the PRAC, it will be critical not to limit data collection only to individuals who are prescribed a continuous regimen as per SmPC, but accept all individuals on any dosing regimen (where local regulations allow to do so) in order to maximize the opportunity to gather important knowledge of the true PrEP usage patterns. Limiting collection of data to be consistent with terms of marketing authorization will exclude the proportion of PrEP users who are prescribed PrEP with other dosing regimens and not provide a full description of PrEP usage. Despite this fact, the registry will retain a noninterventional classification, as the impact of a clinical study on the behavior of both prescribers and participants would be in direct contrast to the main objective of this undertaking to observe the real-life use of Truvada. Country-specific protocols may be developed to comply with local regulations on data collection.

Further and in difference to GVP Module VI collection, management and submission of reports of suspected adverse reactions to medicinal products (revision 2) as specific to commercial sponsors, this protocol proposes to collect only a reduced set of selected safety data. Truvada has been marketed since 2004 and has accumulated over 4 million patient-years of

experience (predominantly in HIV-1 infection). The safety profile is well characterized in clinical studies and through extensive monitoring of post-authorization use. This registry is primarily focused on establishing patterns of use. Collecting all adverse events (AEs) may be of little scientific value and it is feared that the burden of extensive data collection may adversely affect recruitment of both prescribers and participants. This registry will collect selected safety information, ie, fatal events, all serious ADRs, treatment-related bone or renal ADRs, and pregnancies.

# 8. RESEARCH QUESTIONS AND OBJECTIVES

The objectives of this registry are as follows:

- To describe how Truvada for PrEP is prescribed or self-initiated, including the dosing pattern (dose and schedule as daily/intermittent)
- To characterize the demographics of adults and adolescents who are receiving Truvada for PrEP and their HIV risk factors
- To characterize the nature and frequency of individual monitoring after initiating Truvada for PrEP, including any available information on adherence
- To document any cases of new HIV diagnoses and development of any resistance to Truvada and selected safety data
- To summarize the characteristics of healthcare professionals who prescribe Truvada for PrEP

# 9. RESEARCH METHODS

## 9.1. Study Design

This is a prospective, longitudinal, observational, and voluntary participation registry designed to characterize the real-world use of Truvada for PrEP to prevent HIV-1 infections in adults and adolescents in Europe. The individuals who agree to participate in the registry will receive treatment solely based on current clinical practice in the country in which they reside. The use of Truvada for PrEP should be within the conditions of its approved SmPC. However, Gilead will not influence decision making by the participating HCPs or restrict enrollment into the registry to those individuals who are not receiving drug in full compliance with the SmPC (where local regulations allow to do so) as the objective of the registry is to describe the patterns of use and monitoring in real life. Data on intermittent use of Truvada for PrEP will be collected in countries permitting such data collection.

Both male and female adults and adolescents will be recruited for enrollment in the registry. Individuals who started Truvada for PrEP prior to first presenting to the participating HCP or are prescribed Truvada for PrEP will be eligible for enrollment. Baseline will be considered as the start date of Truvada for PrEP. The data for individuals receiving Truvada for PrEP prior to enrollment will be collected retrospectively from the individual's medical record.

Individuals will be followed while on Truvada for PrEP and the frequency of clinic visits will be at the discretion of the prescribers. Individuals will be followed until they are either lost to follow up, discontinued Truvada for PrEP, become infected with HIV, withdraw consent, or registry closure.

Details on Truvada for PrEP use, the healthcare Institution characteristics, and prescriber characteristics will also be collected .

## 9.2. Setting

The registry population will consist of adults and adolescents who are HIV-1 negative and are taking Truvada for PrEP. Individuals who have either self-initiated Truvada for PrEP or have been prescribed Truvada for PrEP and are being monitored while on Truvada for PrEP will be informed about the registry by their HCPs at one of the participating sites. HCPs should assess all users of Truvada for PrEP for inclusion in the registry as they present at the clinic (routine clinic visit) and provide information on the registry if they feel the individual meets the inclusion criteria and does not meet the exclusion criterion. If the individual agrees to participate, they will be required to read, understand, and provide informed consent / assent prior to any registry data collection.

Representative healthcare institutions from countries where Truvada for PrEP are being reimbursed will be recruited to participate in this registry. To facilitate participation with HCPs and users of PrEP, Gilead will leverage its network of investigators who have been a part of prior clinical studies and/or demonstration projects in HIV treatment and PrEP including those doctors

who may not have participated in a study yet but have shown a willingness to learn more about HIV or about antiviral drugs use.

As a supplement to the above, Gilead will work with local key opinion leaders, professional medical organizations & societies and local medical groups who are experienced in the management of HIV infection and prevention (eg, infectious disease specialists).

As part of the registry set up activities, Gilead intends to contact local community groups regarding the registry for Truvada for PrEP.

Due to the restricted availability of Truvada for PrEP in various European countries, this registry will initially be conducted in a limited number of European countries where Truvada for PrEP is being reimbursed. Initially, the target countries to be included in the registry will be Belgium, France, Norway, Portugal, and Sweden. Other countries may be included following reimbursement approval of Truvada for PrEP. The registry will also collect data on HCPs who prescribe Truvada for PrEP.

Recruitment methods within each country will begin by assessing if they have a national policy for PrEP or a similar initiative that would support reimbursement of all HIV-1 PrEP medicinal products or only Truvada or generic equivalents products. HCPs who prescribe products for HIV-1 PrEP will be contacted to determine if they prescribe Truvada for PrEP and if so they will be invited to participate in the registry. Additionally, a review of planned, ongoing, or completed clinical studies or demonstration projects which include Truvada for PrEP will be carried out to identify potential individuals who have completed or discontinued participation in the study but continue to take Truvada for PrEP.

A written contract on the implementation of this registry shall be concluded between sponsor and clinical site. Personnel from the sponsor company or the contract research organization (CRO) will describe the registry to HCPs at each site and provide training on the registry design and data collection to ensure, as much as possible, quality and consistency of data collected. HCPs will only be compensated for their time and efforts on the registry based on current fair market value at the time of contract finalization.

### 9.2.1. Inclusion Criteria:

- HIV-1 negative adults and adolescents who are deemed to be at high risk for acquiring HIV-1

- HIV-1 negative adults and adolescents who provided consent / assent and, depending on local country regulations, parental or legal guardian permission to participate in the registry

- HIV-1 negative adults and adolescents who are receiving Truvada for HIV PrEP, either as a daily or intermittent regimen, and that are clinically monitored

### 9.2.2. Exclusion Criteria:

- Individuals currently participating in a clinical study of HIV PrEP

## 9.3. Variables

The variables to be collected are listed in Table 9-1.

### 9.3.1. Exposure

Data on Truvada for PrEP will be collected. The start and stop dates will be used to estimate person-time of exposure to Truvada. Person-time of exposure will be defined as ([PrEP end date PrEP initiation date] + 1), regardless of temporary interruptions in exposure (< 30 days) and will be expressed in days (recorded in whole days, eg, 41 days). Exposure starts the first day the medication was prescribed or self-initiated (and assumed to have been taken). An individual may have multiple exposures defined as the re-initiation of PrEP after a period of stoppage that is greater than 30 days. Aggregated person-time may also be expressed in person-years ([number of person days]/365.25). Individuals who are taking PrEP on an intermittent or event-driven basis will have exposure calculated in a similar fashion ([PrEP end date PrEP initiation date] + 1).

### 9.3.2. Outcomes

- Describe how Truvada for PrEP is prescribed or self-initiated, including the dosing pattern (dose and schedule as daily/intermittent)
- Characterize the demographics of individuals who were prescribed or are taking Truvada for PrEP and their HIV risk factors
- Characterize the nature and frequency of individual monitoring after initiating Truvada for PrEP, including any available information on adherence
- Document any cases of new HIV diagnoses and development of any resistance to Truvada and any treatment-related renal or bone adverse reactions
- Summarize the characteristics of healthcare professionals who prescribe Truvada for PrEP

### 9.3.3. Items of Surveillance

Data from routine care, as available from medical records, will be collected using electronic case report forms (eCRFs). The following elements will be collected at the approximate intervals as noted in Table 9-1.

**Table 9-1. Data Items and Timing for Surveillance**

| Items of Surveillance | On-Treatment Period | | Seroconversion |
|---|---|---|---|
| | Baseline Truvada PrEP initiation | Each Follow-Up Visit | At Time of New HIV Infection |
| Informed consent | X | | |
| Age | X | | |
| Gender at start of PrEP (Male [M], Female [F], Transgender M-F or F-M) | X | | |
| Weight and Height | X | X | |
| Self-initiated or prescribed Truvada for PrEP usage details (dose and schedule [continuous/daily or intermittent]) | X | X | |
| Truvada for PrEP start and stop dates or duration of PrEP usage | X | X | X |
| Product name: (Truvada prescribed or self-sourced) | X | X | X |
| Assessment of adherence with PrEP | X | X | X |
| Risk factors for HIV-1 | X | X | X |
| Use of recreational drugs during sex | X | X | X |
| Sexual transmitted infections – (1) oropharyngeal, (2) urethral/cervicovaginal, (3) rectal, and (4) syphilis | X | X | X |
| HIV-1 test method(s), results, and dates | X | X | X |
| Prior use of PrEP (prescribed or self-medicated) or PEP | X | | |
| HBV serostatus | X | | |
| HCV serostatus | X | | |
| If female, pregnancy status | X | X | X |
| eGFR | X | X | |
| Serum phosphate | X | X | |
| Safety data (all fatal Events and all serious adverse drug reactions [SADRs], treatment-related renal or bone adverse drug reactions, and pregnancy reports) | X | X | X |

| Items of Surveillance | On-Treatment Period | | Seroconversion |
|---|---|---|---|
| | Baseline Truvada PrEP initiation | Each Follow-Up Visit | At Time of New HIV Infection |
| Possible factors leading to new HIV infection | | | X |
| Genotypic resistance testing | | | X |
| Reason for PrEP discontinuation | | X | X |

Data on participating institutions and prescribers will be collected at the time of enrollment. Institution information will include country, city, and type of institution. Prescriber information will include medical specialty.

### 9.3.4. Laboratory Tests

Routinely collected laboratory values and date(s) of test(s) will be captured as available. This registry will collect:

- Virologic testing (HIV test methodology and results, hepatitis B serology, hepatitis C serology)
- Renal function (estimated glomerular filtration rate [eGFR]), serum phosphate
- Genotypic resistance testing (testing results)
- Pregnancy testing (testing results)

### 9.3.5. Variables Collected in the Event of Discontinuation of PrEP

The reason for and the date of PrEP discontinuation will be collected. If the reason for discontinuation is related to a serious adverse drug reaction (SADR) or treatment-related renal or bone adverse reactions, this will be collected in the AE section of the eCRF. If the discontinuation is due to a withdrawal of consent, no further data will be collected. If the discontinuation is due to development of a new HIV-1 infection (ie, seroconversion), the results of any HIV diagnostic testing and genotypic resistance testing should be reported both in the registry and to the applicable country central database for HIV testing and diagnosis. Information on adherence to Truvada for PrEP along with possible factors leading to HIV-1 seroconversion should be reported.

### 9.3.6. Variables Collected in the Event of Loss to Follow-up

If an individual is lost to follow-up, a notation will be made on the eCRF as to the reason for the loss to follow-up, if known.

### 9.3.7. Site Information

Data will be collected about the sites which prescribe and/or monitor Truvada for PrEP. Data will include location (eg, country, city, urban or rural) and setting (eg, hospital, clinic, private practice). Additional data on current practice for providing Truvada for PrEP will be collected for the sites that agree to participate in the registry.

## 9.4. Data Sources

This observational noninterventional registry will extract data from the individual's medical record. Data obtained from clinic visits, physical examinations, and medical records, including medical history, hepatitis history, prescribed medications, laboratory results, and safety data, will be captured while participating in the registry. HCPs will enter data into eCRF at each data collection point in a timely manner. If the HCP receives queries about data entered in the eCRF from the sponsor (or designee), the HCP will review the medical record and correct the eCRF data if necessary.

## 9.5. Study Size

The purpose of the registry is to provide insight into the patterns of Truvada for PrEP usage and how clinicians are monitoring individuals on Truvada for PrEP. The registry is not designed or powered to compare rates of seroconversion or adherence with studies or demonstration projects.

Enrollment will be open to both adults and adolescents, and enrolled individuals will be followed while Truvada for PrEP is continued. Target is to enroll and follow enough adults to provide at least 400 person-years of follow-up data and enough adolescents to provide at least 25 person-years of follow-up data.

## 9.6. Data Management

After finalization and approval of the protocol, an eCRF will be built in a commercial electronic data capture (EDC) system to collect the data listed in the variables section (Table 9-1). Personal identifying data such as names, health record identifiers, and national insurance numbers will not be collected.

HCP participants from each site will receive a unique username and password from the EDC system administrator following completion of the EDC system training. Completion of training and receipt of username/password will allow sites to enter data into the eCRF. HCPs will electronically sign the eCRF to confirm responsibility for the data following completion of data entry and data quality activities. Registry data will be stored on secure network drives with access restricted to authorized personnel only.

## 9.7. Data Analysis

Descriptive data analysis will be used to summarize the available data. There are no statistical hypotheses to evaluate. Categorical variables will be reported by proportions and continuous variables will be reported by mean, standard deviation, minimum, median, and maximum. Prescriber characteristics will be summarized. Demographics and clinical characteristics of individuals on Truvada for PrEP will be analyzed. The products prescribed and available prescription details, the frequency of monitoring, and any relevant data on adherence monitoring will be summarized. Seroconversion cases and results of resistance testing will be summarized. Reports of treatment-related renal and bone adverse drug reactions (SADRs and ADRs) will be summarized. Females participants in the registry who are pregnant will also be analyzed.

Data will be presented overall, and by age group (adolescents and young adults) and risk factors for HIV transmission.

Rates of adherence and new HIV diagnoses (i.e., seroconversion) will be calculated with 95% confidence intervals. Results will be presented overall and by subgroups including adults and adolescents, gender, and country.

Comprehensive information relating to the analysis of this registry will be provided in the statistical analysis plan.

## 9.8. Quality Control

To ensure the quality and integrity of the registry results, the EDC tool will include automatic data validation checks and the sponsor and/or contracted third party will perform remote manual data quality review in accordance with the registry data quality and monitoring documents. In addition, monitors will engage sites with regard to data quality and completeness both at the Site Initiation Visit with training on eCRF completion, via routine telephone calls and may perform onsite visits, as documented in the registry monitoring plan. The HCP agrees to respond to the resulting queries in a timely manner to enable the timely collation of the analysis datasets.

## 9.9. Limitations of the Research Methods

Limitations of this registry are those common to registries, including selection bias that may limit generalizability to the general PrEP using population.

HCPs and their respective institutions must volunteer and agree to participate in the registry and thus may not be representative of all prescribers of Truvada in Europe. Uninfected individuals receiving Truvada for PrEP must also agree to participate in the registry and thus also may not be representative of all PrEP users. The ability for individuals to obtain Truvada for PrEP by the internet further complicates this issue as it is challenging to monitor or compare these individuals with those who can obtain the drug and who volunteer to participate in the registry.

As this registry may enroll HCPs and institutions less familiar with registry data collection processes or may have fewer resources available to provide data to the registry, the extent and quality of the data may be compromised. To facilitate collection of data, this registry will reduce the extent of data collected and also provide standard training at the Site Initiation Visit on how to complete the eCRF. One example is rather than collecting all AEs, this registry is proposing to collect only fatal Events, SADRs, treatment emergent renal or bone ADRs, and pregnancy reports.

Collecting data on use of Truvada for PrEP may result in data that are different from the usual manner of prescribing in accordance with the SmPC. For example, Truvada for PrEP is recommended to be taken daily. However, other dosing regimens, such as event-based dosing, may be prescribed.

Enrollment of adolescents will present additional challenges. Adolescents may be prescribed Truvada for PrEP but may choose not to participate in the registry. Participation will be further limited if parenteral informed consent is required. In the United States, prior to the broadening of the approval to include use in adolescents, drug utilization data suggested adolescents using Truvada for PrEP accounted for approximately 1.5% of Truvada for PrEP usage {Magnuson et al 2018}. Efforts will be made to enroll as many adolescents as possible; however, enrollment of a pre-established minimum recruitment number for adolescents may not be achievable.

## 9.10. Other Aspects

### 9.10.1. Joint HCP/Sponsor Responsibilities

#### 9.10.1.1. Access to Information for Monitoring

The registry monitor is responsible for routine review of the eCRFs at regular intervals throughout the duration of the registry to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the forms. Monitoring will be conducted as outlined in the registry monitoring plan.

#### 9.10.1.2. Registry Discontinuation

Both Gilead and a participating HCP reserve the right to terminate participation in the registry at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and independent ethics committees (IECs), where applicable.

As this registry is conducted for a commitment to a regulatory authority, any consideration for termination of the registry will be discussed with the applicable authority beforehand.

# 10. PROTECTION OF HUMAN SUBJECTS

## 10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The HCPs will conduct this registry in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) GVP including archiving of essential documents.

## 10.2. Independent Ethics Committee Review

The sponsor or delegate will submit this protocol and any accompanying material to be provided to the individual (such as advertisements, individual information sheets, or descriptions of the registry used to obtain informed consent) to an IEC. The HCP will not begin any study activities until approval from the IEC has been documented and provided as a letter to the HCP.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the individual after initial IEC approval will also be submitted for IEC approval prior to its use, with the exception of those necessary to reduce immediate risk to registry individuals.

## 10.3. Informed Consent

Participating HCPs are responsible for obtaining written informed consent from each individual participating in this registry after adequate explanation of the aims, methods, objectives, and potential hazards, and alternatives of the registry prior to registry participation and before performing any registry-related activities. The HCP must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the individual or the individual's legally authorized representative and the person conducting the consent discussion, and by an impartial witness if required by IEC or local requirements.

## 10.4. Confidentiality

Participating HCPs must assure that individuals' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. A unique individual identifier will be used and only the site (not Gilead/CRO) will be able to trace that number back to the individual's records.

# 11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This study is a post-authorization (safety) study and will collect required safety information as described in Section 11.1.1. Details for the Gilead global pharmacovigilance system through which all safety data are being managed are described in the Pharmacovigilance Masterfile, particularly in the Pharmacovigilance System Master File (PSMF) Module on Pharmacovigilance processes.

## 11.1. Investigator Instructions for Collecting and Reporting Selected Safety Information to Gilead

### 11.1.1. Safety Information to be Collected

Safety information is required to be collected and reported for this registry from the time of the patient's consent to participate in the registry (ie, signing informed consent) until up to 4 weeks after completion of Truvada for HIV-1 PrEP or early discontinuation of Truvada, loss of follow-up, or withdrawal of consent. Safety information to be collected includes a description of the AE, start and stop dates, severity, causality, and other relevant medical information.

The safety profile for Truvada has been well characterized in clinical studies and post marketing experience. Considering the main goal of this registry, aiming to achieve consistency and simplicity in data collection and reporting without undue burden on the investigators, this registry is designed to collect and analyze the following safety information in individuals taking Truvada for PrEP:

- Fatal Events
- All SADRs
- Treatment emergent renal or bone ADRs
- Pregnancy reports (maternal pregnancy and partner pregnancy)

Timelines for reporting to the registry are as follows:

- Within 3 calendar days of knowledge of all fatal Events (regardless of causality) and SADRs
- Within 30 calendar days of treatment emergent renal or bone ADRs
- Within 30 calendar days of knowledge of a pregnancy

### 11.1.2. Timelines for Reporting Safety Information

- Site personnel must record specified safety information in the eCRF database and transmit them to Gilead Pharmacovigilance and Epidemiology (PVE) within the timelines specified in Section 11.1.1. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the safety information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the event on the paper report form (ie, the Non-Interventional Study AE/SAE Report Form or Non-Interventional Study Special Situations Report Form) and submit by email or fax to:

| | | |
|---|---|---|
| Gilead PVE: | Fax: | PPD |
| | Email: | PPD |

- As soon as it is possible to do so, any safety event reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If a safety event has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

### 11.1.3. Instructions for Reporting Pregnancies

The following information is required to be collected and reported for this study if an individual becomes pregnant while taking Truvada for PrEP:

- Information on all pregnancies

- The outcome of the pregnancy, including any premature termination (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons)

Timelines for reporting to Gilead are as follows:

- Within 30 calendar days of knowledge of the pregnancy

- Within 3 calendar days of knowledge of all pregnancy related serious events (regardless of causality, eg, a spontaneous abortion, hospitalization, etc.)

If reporting of pregnancies is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning.

Pregnancy information should be also reported on the paper pregnancy report form, and the outcome should be reported on pregnancy outcome report form. However, if the event qualifies as a SAE then an SAE form should be used to report the event

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) or SAE occurring as an adverse pregnancy outcome poststudy must be reported with the 3-calendar-day timelines.

## 11.2. Reporting Requirements to Regulatory Authorities

Gilead is responsible for analyzing reports of collected safety information and reporting to regulatory agencies as determined by country-specific legislation or regulations.

Assessment of expectedness for all safety reports will be determined by Gilead using reference safety information specified in the product label.

Participating HCPs are encouraged to report all suspected ADRs to the national pharmacovigilance systems.

## 11.3. Definitions

### 11.3.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history eCRF (if applicable).

### 11.3.2. Adverse Drug Reactions

An ADR is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

### 11.3.3. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the individual was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused fatal events if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the individual or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

### 11.3.4. Serious Adverse Drug Reaction

A SADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

## 11.4. Clinical Laboratory Abnormalities

Laboratory abnormalities without clinical significance and considered enot to be related with the medicinal product are not recorded as safety events. However, serious laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) or nonserious renal or bone related laboratory abnormalities that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation and considered to be causally associated with the medicinal product must be recorded as an ADR, or an SADR, if applicable.

In addition, serious laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) or nonserious renal or bone related laboratory or other abnormal assessments that are associated with signs and/or symptoms must be recorded as an ADR or SADR if they meet the definition of an ADR or SADR as described in Section 11.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

## 11.5. Assessment of Causality for Study Drugs

The investigator or qualified sub-investigator is responsible for assessing the causal relationship to drug therapy for each event and using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes:** There is a reasonable possibility that the event may have been caused by the medicinal product (and thus reported as an ADR or an SADR).

It should be emphasized that ineffective treatment should not be considered as causally related in the context of reporting safety information.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING REGISTRY RESULTS

## 12.1. Registry Report and Publications

The interim analysis reports will be prepared annually after opening enrollment and submitted within 60 days.

Data collection will stop 6 months after the last individual has been recruited during the 3-year enrollment period. A final report will be submitted within 12 months and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on GVP Module VIII. Note that an abbreviated report may be prepared in certain cases.

Gilead shall communicate to the European Medicines Agency and the competent authorities of the Member States in which participating research institutions are taking part in the registry; the final manuscript within 2 weeks after first acceptance for publication.

# 13. REFERENCES

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World Health Organization (WHO). Module 12: Adolescents and Young Adults - WHO Implementation Tool for Pre-Exposure Prophylaxis (PrEP) of HIV Infection. July. 2018b.

# 14. APPENDICES

## Annex 1. ENCePP Checklist for Study Protocols

| **Study title:**<br>A Prospective, Longitudinal, Observational Registry of Truvada for HIV-1 Pre-Exposure Prophylaxis (PrEP) of Adults and Adolescents in Europe |
|---|

| **Study reference number:** GS-EU-276-4487 |
|---|

| **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] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Study progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results | ☒ | ☐ | ☐ | 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 8 |
| 2.1.1 Why the study is conducted? (eg to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 7.1 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 9 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |

[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.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| This registry is a purely descriptive and no hypothesis testing is proposed. |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (eg. cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.4 |
| 3.3 Does the protocol specify measures of occurrence? (eg. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.7 |
| 3.4 Does the protocol specify measure(s) of association? (eg. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☐ | ☐ | ☒ | |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

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|---|
| |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 6.0 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.1 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.1 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.1 |
| 4.2.5 Duration of follow-up? | ☒ | ☐ | ☐ | 9.1 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (eg. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.1 |

Comments:

| |
|---|
| |

| **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? (eg. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (eg. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 Is exposure classified according to time windows? (eg. current user, former user, non-use) | ☐ | ☐ | ☒ | |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| PK information is not a requirement for this registry. |

| **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? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.3 |
| 6.3 Does the protocol address the validity of outcome measurement? (eg. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| There are no health technology assessment considerations being made as part of this registry. |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☐ | ☐ | ☒ | |
| 7.1.1. Does the protocol address confounding by indication if applicable? | ☐ | ☐ | ☒ | |
| 7.2 Does the protocol address: | ☐ | ☐ | ☒ | |
| 7.2.1. Selection biases (eg. healthy user bias) | ☐ | ☐ | ☒ | |
| 7.2.2. Information biases (eg. misclassification of exposure and endpoints, time-related bias) | ☐ | ☐ | ☒ | |
| 7.3 Does the protocol address the validity of the study covariates? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| This registry is descriptive and no casual effect relationship is being tested and no modeling is being proposed in terms of estimation of outcome measures. |

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

Comments:

| |
|---|
| This registry is descriptive and no casual effect relationship is being tested and no modeling is being proposed in terms of estimation of outcome measures. |

| **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? (eg. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.4 |
| 9.1.2 Outcomes? (eg. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.1.3 Covariates? | ☐ | ☐ | ☒ | |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (eg. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.4 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.2.2 Outcomes? (eg. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.4 |
| 9.2.3 Covariates? (eg. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.4 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (eg. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | |
| 9.3.2 Outcomes? (eg. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | |
| 9.3.3 Covariates? | ☐ | ☐ | ☒ | |
| 9.4 Is a linkage method between data sources described? (eg. based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| There are no linkages to external data sources. |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.3 Are stratified analyses included? | ☐ | ☒ | ☐ | |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☐ | ☐ | ☒ | |
| 10.5 Does the plan describe methods for handling missing data? | ☐ | ☐ | ☒ | |
| 10.6 Is sample size and/or statistical power estimated? | ☐ | ☒ | ☐ | |

Comments:

| |
|---|
| |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (eg. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| Independent review of the registry results is not deemed appropriate as it is primarily concerned with drug utilization. |

| **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? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (eg. 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? (eg. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9 |

Comments:

| |
|---|
| |

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10.2 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10.4 |

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? | ☒ | ☐ | ☐ | 2 |

Comments:

| |
|---|
| |

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (eg. to regulatory authorities)? | ☒ | ☐ | ☐ | 12.1 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12.1 |

Comments:

| |
|---|
| Publication plans have not been determined at this time. |

Name of the main author of the protocol: PPD

Date:

Signature: _____

## Annex 2. Study Acknowledgement

**Gilead Sciences, Inc.**
**333 Lakeside Drive**
**Foster City, CA 94404**

**A Prospective, Longitudinal, Observational Registry of Truvada for HIV 1 Pre-Exposure Prophylaxis (PrEP) of Adults and Adolescents in Europe**

Original: 21 March 2018

Version 1.1: 17 August 2018

Version 1.2: 28 March 2019

Version 1.3: 20 August 2019

Version 1.4: 20 January 2020

This protocol has been approved by Gilead Sciences Europe, Ltd. The following signatures document this approval.

PPD
Gilead Study Director (Printed)
Author

Signature

Date

PPD
Gilead EU QPPV (Printed)

Signature

Date

## HEALTHCARE PROFESSIONAL STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

| | |
|---|---|
| Principal HCP Name (Printed) | Signature |
| Date | Site Number |